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ARCHIVES of INTERNAL MEDICINE

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# RESULTS IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS

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AND
NED McKRILL, M.D.†
NEW ORLEANS

RESULTS in the treatment of subacute bacterial endocarditis with a wide variety of therapeutics measures were uniformly unsuccessful prior to the advent of the newer chemotherapeutic drugs. Methods of therapy in recent years have included the use of arsenicals as employed by Osgood,[1] heparin alone,[2] sulfonamide compounds in usual[3] and massive dosages,[4] sulfonamide drugs and heparin,[5] sulfonamide drugs and artificial fever induced by typhoid vaccines[6] or by physical measures, and penicillin alone and in combination with heparin. Lichtman,[7] in reviewing 704 cases (fig. 1), found 1 per cent of spontaneous cures. Of 489 patients treated by sulfonamide chemotherapy, 21 recovered, an incidence of 4 per cent; of 109 heparinized, 7 (6.5 per cent) recovered; of 61 patients given artificial fever therapy, 4 (6.5 per cent) recovered; of 45 patients treated with chemotherapy and intravenously injected typhoid vaccine, 7 (15.5 per cent) recovered.

From the Department of Medicine, Louisiana State University School of Medicine, and the Charity Hospital of Louisiana at New Orleans.

† Deceased.

1. Osgood, E. E.: Neoarsphenamine Therapy of Bacterial Infections, Arch. Int. Med. **69**:746 (May) 1942.

2. Friedman, M.; Hamburger, W. W., and Katz, L. N.: The Use of Heparin in the Therapy of Subacute Bacterial Endocarditis, J. A. M. A. **113**:702 (Nov. 4) 1939.

3. Field, H.; Hoobler, S. W., and Avery, N. C.: Results of Chemotherapy in Subacute Bacterial Endocarditis, Am. J. M. Sc. **202**:798, 1941.

4. Dick, G. F.: Subacute Bacterial Endocarditis: Recovery Following Intravenous Sodium Sulfadiazine, J. A. M. A. **120**:24 (Sept. 5) 1942.

5. Kelson, S. R.: New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination: Preliminary Report, J. A. M. A. **113**:1700 (Nov. 4) 1939.

6. Solomon, H. A.: Subacute Bacterial Endocarditis: Treatment With Sulfapyridine and Intravenous Injections of Typhoparatyphoid Vaccines, New York State J. Med. **41**:45, 1941.

7. Lichtman, S. S.: Treatment of Subacute Bacterial Endocarditis: Current Results, Ann. Int. Med. **19**:787, 1943.

Heparin was first employed in the treatment of endocarditis by Friedman, Hamburger and Katz,[2] and Kelson and White.[8] Katz and Elek[9] concluded from their series treated with heparin and chemotherapy that the use of heparin should be abandoned. They administered heparin to a patient for six weeks without ill effects. Friedman,[10] Blumer,[11] and Smith, Sauls and Stone[12] have also expressed their

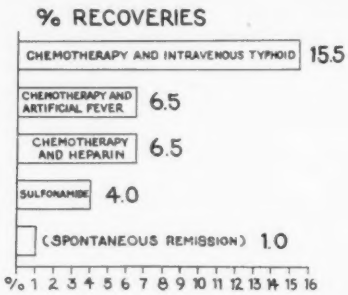


Fig. 1.—Results in the treatment of subacute bacterial endocarditis reported by Lichtman.

TABLE 1.—*Results of Treatment of Subacute Bacterial Endocarditis with Penicillin Reported by Other Authors*

| Author | Number of Cases | Number of Probable Cures |
|---|---|---|
| Florey and others [17] | 1 | 1 |
| Keefer, C. S.[16] | 55 | 3 |
| Herrell and others [18] | 4 | 0 |
| Roy, B. B.[19] | 17 | 3 |
| Collins, B. C.[20] | 1 | 1 |
| Bloomfield and others [21] | 10 | 8 |
| Pizzi and associate [22] | 1 | 1 |
| Dawson and associate [14] | 27 | 21 |
| White and others [23] | 9 | 6 |
| Loewe [24] | 54 | 40 |
| Kelson [25] | 1 | 1 |
| Harford and others [26] | 3 | 2 |
| Paullin and associate [27] | 6 | 3 |
| Meads and others [15] | 9 | 7 |
| Evans [27] | 4 | 1 |
| Russek and others [28] | 2 | 2 |
| Seabury [29] | 12 | 8 |
| Traut, E. F.[30] | 1 | 1 |
| Goerner [32] | 16 | 11 |
| Bloomfield and others [33] | 11 | 10 |
| Hines and associate [34] | 2 | 0 |
| Flippin and others [31] | 20 | 16 |
| Levy and associate | 11 | 8 |
| Total | 277 | 154 (55.6%) |

8. Kelson, S. R., and White, P. D.: Notes on 250 Cases of Subacute Bacterial (Streptococcal) Endocarditis Studied and Treated Between 1927 and 1939, Ann. Int. Med. **22**:40, 1945.

9. Katz, L. N., and Elek, S. R.: Combined Heparin and Chemotherapy in Subacute Bacterial Endocarditis, J. A. M. A. **124**:149, (Jan. 15) 1944.

10. Friedman, M.: The Use of Sulfanilamide and Sulfapyridine in the Therapy of Subacute Bacterial Endocarditis, Arch. Int. Med. **67**:921 (May) 1941.

opinion that the proved dangers of heparin therapy outweigh its unproved advantages. Lichtman in his review found a 6.5 per cent recovery rate with chemotherapy and heparin, a 2.5 per cent increase as compared to those cases in which chemotherapy alone was used.

Successful penicillin therapy in a series of cases of subacute bacterial endocarditis was first reported by Loewe and others [13] in January 1944. Dawson and Hunter [14] employed combined penicillin and heparin therapy in the majority of their 20 cases. Hemorrhagic complications resulting from heparinization were definitely observed in only 1 instance. Penicillin and heparin were employed in 5 of the 16 cases reported by Meads and his associates.[15] They concluded that no additional benefit was derived from its use. Hemorrhagic manifestations, noted by Meads during the administration of penicillin and heparin, occurred in 4 patients during treatment with penicillin alone. If we combine the cases reported by Keefer,[16] Florey,[17] Herrell,[18] Roy,[19] Collins,[20] Bloomfield,[21] Pizzi,[22] Dawson,[14] White,[23] Loewe,[24] Kelson,[25] Harford,[26]

11. Blumer, G.: Subacute Bacterial Endocarditis, Medicine **2**:105, 1923.

12. Smith, C.; Sauls, H. C., and Stone, C. F.: Subacute Bacterial Endocarditis Due to Streptococcus Viridans, J. A. M. A. **119**:478 (June 6) 1942.

13. Loewe, L.; Rosenblatt, P.; Greene, H. J., and Russell, M.: Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis: Report of Seven Consecutive Successfully Treated Patients, J. A. M. A. **124**:144 (Jan. 15) 1944.

14. Dawson, M. H., and Hunter, T. H.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. A. M. A. **127**:129 (Jan. 20) 1945.

15. Meads, M.; Harris, H. W., and Finland, M.: The Treatment of Bacterial Endocarditis with Penicillin, New England J. Med. **232**:463, 1945.

16. Keefer, C. S., in discussion on papers of Dawson and Hobby, Herrell, Bloomfield, Rantz and Kirby and Dubos, J. A. M. A. **124**:636 (March 4) 1944.

17. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, Lancet **1**:387, 1943.

18. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with Analysis of 150 Cases in Which It Was Employed, J. A. M. A. **125**:1202 (Aug. 26) 1944.

19. Roy, B. B.: Chemotherapy of Bacterial Invasion by Antibacterial Substances of Bacteria and Moulds with Special Reference to Penicillin, J. Indian M. A. **13**:309, 1944.

20. Collins, B. C.: Subacute Bacterial Endocarditis Treated with Penicillin, J. A. M. A. **126**:233 (Sept. 23) 1944.

21. Bloomfield, A. L.; Kirby, W. M. M., and Armstrong, C. D.: A Study of "Penicillin Failures," J. A. M. A. **126**:685 (Nov. 11) 1944.

22. Pizzi, F. W., and McCarthy, F. W.: Subacute Bacterial Endocarditis Sucessfully Treated with Penicillin, U. S. Nav. M. Bull. **43**:1010, 1944.

23. White, P. D.; Mathews, M. W., and Evans, E.: Notes on the Treatment of Subacute Bacterial Endocarditis Encountered in 88 Cases at the Massachusetts General Hospital During the Six Year Period 1939 to 1944 (Inclusive), Ann. Int. Med. **22**:61, 1945.

*(Footnotes continued on next page)*

Paullin,[27] Meads,[15] Evans,[27] Russek,[28] Seabury,[29] Traut,[30] Flippin,[31] Goerner,[32] Bloomfield,[33] Hines,[34] and Levy (table 1), there is a total of 154 (55.6 per cent) possible cures in 277 of the cases of subacute bacterial endocarditis treated with penicillin.

### METHODS OF TREATMENT AND RESULTS IN THE CHARITY HOSPITAL

Table 2 shows the results that we secured at the Charity Hospital in the treatment of subacute bacterial endocarditis prior to the use of penicillin and heparin. Endocarditis was the cause of death in 0.6

TABLE 2.—*Results of Treatment in the Charity Hospital Prior to Penicillin Therapy*

| | Cases | Successes | Failures |
|---|---|---|---|
| Supportive care alone | 35 | 0 | 35 |
| Sulfanilamide | 20 | 0 | 20 |
| Sulfadiazine | 40 | 0 | 40 |
| Other sulfonamide drugs | 15 | 0 | 15 |
| Sulfadiazine and fever | 7 | 0 | 7 |
| Sulfadiazine, massive dosage | 4 | 0 | 4 |
| Massive arsenotherapy | 3 | 0 | 3 |

24. Loewe, L.: The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis, Canad. M. A. J. **52**:1, 1945; The Combined Use of Anti-Infectives and Anticoagulants in the Treatment of Subacute Bacterial Endocarditis, Bull. New York Acad. Med. **21**:59, 1945.

25. Kelson, S. R.: Observations on the Treatment of Subacute Bacterial (Streptococcal) Endocarditis Since 1939, Ann. Int. Med. **22**:75, 1945.

26. Harford, C. G.; Martin, S. P.; Hageman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococci, Pneumococci, Gonococci and Other Infections With Penicillin, J. A. M. A. **127**:325, (Feb. 10) 1945.

27. Evans, quoted by Paullin, J. E., and McLoughlin, C. J.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, Ann. Int. Med. **22**:475, 1945.

28. Russek, H. I.; Smith, R. H., and Derman, H.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, Ann. Int. Med. **22**:863, 1945. Russek, H. I.; Smith, R. H., and Zohman, B. L.: Subacute Bacterial Endocarditis Complicated by Agranulocytosis: Report of Case with Recovery, ibid. **22**:867, 1945.

29. Seabury, J. H.: Personal communication to the authors.

30. Traut, E. F.: Treatment of Subacute Bacterial Endocarditis: Recovery with Penicillin, Illinois M. J. **88**:24, 1945.

31. Flippin, H. F.; Mayock, R. L.; Murphy, F. D., and Wolferth, C. C.: Penicillin in the Treatment of Subacute Bacterial Endocarditis, J. A. M. A. **129**:841 (Nov. 24) 1945.

32. Goerner, J. R.; Geiger, A. J., and Blake, F. G.: Treatment of Subacute Bacterial Endocarditis with Penicillin: Report of Cases Treated Without Anticoagulant Agents, Ann. Int. Med. **23**:491, 1945.

33. Bloomfield, A. L.; Armstrong, C. D., and Kirby, W. M.: The Treatment of Subacute Bacterial Endocarditis with Penicillin, J. Clin. Investigation **24**:251, 1945.

34. Hines, L. E., and Kessler, D. L.: The Effect of Penicillin on Heparin Tolerance, J. A. M. A. **128**:794 (July 14) 1945.

per cent of 8,313 cases in which autopsies were performed from 1935 to 1940 inclusive and in 5 per cent of the deaths due to heart disease. During the six and a half year period beginning in 1938, there were 112 clinical cases, or an approximate incidence of 1 in every 3,500 hospital admissions. Prior to the institution of penicillin and heparin therapy, there were no recoveries with supportive therapy, sulfonamide compounds in massive doses or arsenotherapy. Various other methods were used in a few cases not recorded.

Our original plan of treatment of subacute bacterial endocarditis consisted of the simultaneous administration of penicillin, heparin and sulfadiazine. Nine of our 11 patients received heparin dissolved in 1,000 cc. of a 5 per cent solution of dextrose in distilled water as a continuous intravenous drip along with penicillin intramuscularly for the initial two weeks of treatment. The amount of heparin given intravenously required to maintain a clotting time between thirty to sixty minutes for twenty-four hours has varied from 90 to 300 mg. (9 to 30 cc.). It has been our custom to dissolve one half of the estimated amount of heparin in a liter of a 5 per cent solution of dextrose in distilled water and start this as an intravenous drip. Regulation of the clotting time is then carried out by speeding or slowing the infusion, adding heparin to the infusion if the clotting time is low or connecting the solution of 5 per cent dextrose in distilled water without heparin to the infusion set if the clotting time is too high. In this manner the patient receives 2,000 cc. of fluid intravenously daily. We attempt to limit oral fluids during heparinization. The employment of penicillin and heparin in our infusions has not prevented the occasional occurrence of thrombophlebitis and the frequent occurrence of phlebothrombosis.

We have experienced frequent reactions during heparinization, occurring daily in some patients. These reactions are characterized by fever, sometimes with a temperature up to 108 F., chills, mild excitement and some disorientation. In an attempt to evaluate the etiologic agents responsible for these reactions, we have alternated the following procedures when patients experienced reactions: We have continued the infusion, utilizing the same tubing but employing a fresh bottle of heparin with a 5 per cent solution of dextrose in distilled water. We continued to utilize the same bottle of heparin with the dextrose in distilled water and changed the tubing, changed the site of the infusion, utilizing the same tubing with the 5 per cent solution of dextrose in distilled water without heparin, stopped the infusion and used various other modifications. All of these procedures were evaluated on each patient when he had a reaction, if the reaction was not too severe. If a severe reaction occurred the infusion was discontinued until the patient completely recovered, at which time it was again begun. These reactions did not necessitate permanent discontinuance of heparin in any

case, although it made clotting times irregular in some. From these studies it was concluded that varying factors come into play in causing these reactions. Some are pyrogenic reactions due to the release of protein from the decomposition of bacteria or to other foreign protein matter present in the infusion apparatus or infusion fluids. Some are due to heparin sensitivity, some are due to embolic phenomena, and some are not explainable. Undoubtedly the continuous flow of heparin and fluid over a piece of tubing for four days will tend to dislodge every minute particle of foreign matter from the tubing. Probably during the ordinary course of four hours with the same infusion set a reaction would not occur. It is difficult to determine the exact cause of the reaction in many cases, and if the reaction becomes too severe the infusion is temporarily discontinued. We have had only 1 case in our series in which deleterious effects may have been due to heparin.

Many of the unfortunate reactions occurring during heparinization are due to inadequate supervision of its administration. Determination of clotting time by the Lee and White method [35] should be made three times daily during the period of heparinization. The clotting time in 1 patient was eight minutes by other methods and sixty minutes by this method. We endeavor to maintain a clotting time between thirty and sixty minutes for a period of two weeks. The danger from overheparinization is greater from the tenth to the fourteenth day, that is, in the latter part of the treatment, than it is during the earlier part of the heparinization. If the clotting time rises to two hours during the first few days of treatment no serious consequences are likely to occur. However, later in the treatment elevated clotting times above sixty minutes are to be avoided. During the last few days of heparinization we try to keep the clotting time at the lower level of the margin of safety, that is, around thirty minutes. We have had no experience with heparin modified in various mediums, such as Pitkin menstruum, for subcutaneous implanation as utilized by Loewe and others.[36]

We have employed penicillin in varying dosages. At first we had to use smaller doses due to our limited supply. We realized the need for larger dosages than we were employing; however, an adequate supply of penicillin was not available to us for the treatment of subacute bacterial endocarditis when the initial portion of this work was started. Earlier we utilized the intravenous route of administration of penicillin, using heparin and penicillin in the same infusion. Because of the reactions to heparin, we frequently had to discard a bottle containing penicillin and heparin. Separate infusions of penicillin and of

35. Gradwohl, R. B. H.: Clinical Laboratory Methods, ed. 3, St. Louis, C. V. Mosby Company, 1943, p. 514.

36. Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin: Preliminary Report, Am. J. M. Sc. **208**:54, 1944.

heparin would render the treatment too undesirable both for the patient and for the physician. The incidence of thrombosis is increased when penicillin is used intravenously. As shown by Cowan,[37] some samples of rubber tubing inactivate some of the penicillin in the solution, especially when the penicillin is kept in contact with the rubber tubing for several hours. These reasons led us to the discontinuation of the intravenous route and the utilization of the intramuscular route, which rendered the treatment relatively simple except for the initial two weeks of heparinization. Penicillin was given in divided doses every two hours intramuscularly, in amounts varying from a total of 100,000 to 200,000 units daily. Two hour administration maintains a satisfactory constant level of penicillin.[38] We occasionally noted local reactions at the site of injection; these have become rare with the newer supply of penicillin. Penicillin levels in the blood were not determined. We did not perform penicillin sensitivity tests on the organisms isolated from our patients.

Sulfadiazine in a dosage of 1 Gm. every four hours day and night was employed along with penicillin and heparin. This was used because of the potentiation in the effect of penicillin noted by Rammelkamp,[38] Ungar,[39] and others [40] when its use was combined with the simultaneous administration of sulfadiazine. Daily urinalyses and triweekly complete blood counts were made, and the patients were watched closely for any signs of reaction to the sulfonamide drugs. The only reaction noted was a mild leukopenia in 1 case, which cleared rapidly on the discontinuation of the sulfonamide drug. Occasionally we kept our patients on a small maintenance dosage of sulfadiazine (1 Gm.) for a period of months following completion of treatment.

Figure 2 demonstrates our earlier plan when a limited amount of penicillin was available. Treatment was given for only fourteen days, 200,000 units of penicillin being given every twenty-four hours by continuous intravenous drip. During the first ten days, heparinization by continuous intravenous drip of 100 to 200 mg. of heparin for twenty-four hours was given in order to maintain the clotting time above thirty minutes.

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37. Cowan, S. T.: Effect of Rubber Tubing on Solutions of Penicillin, Lancet **1**:178, 1945.

38. Rammelkamp, C. H., and Keefer, C. S.: Penicillin: Its Antibacterial Effect in Whole Blood and Serum for the Hemolytic Streptococcus and Staphylococcus Aureus, J. Clin. Investigation **22**:649, 1943.

39. Ungar, J.: Synergistic Effect of Para-Aminobenzoic Acid and Sulfapyridine on Penicillin, Nature, London **152**:245, 1943.

40. Bigger, J. W.: Synergic Action of Penicillin and Sulphonamides, Lancet **2**:142, 1944.

Figure 3 demonstrates the method employed in our later cases. Twelve thousand units of penicillin was administered day and night every two hours by intramuscular injections and was continued for twenty-eight days. Over this same period 1 Gm. of sulfadiazine was given every four hours day and night. Heparinization was accomplished during the first fourteen days by the same technic used in our previous cases. At present we are employing the method depicted in figure 3 with one modification: The dosage of penicillin has been increased to

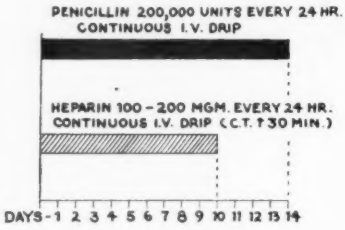
PENICILLIN 200,000 UNITS EVERY 24 HR.
CONTINUOUS I.V. DRIP
HEPARIN 100-200 MGM. EVERY 24 HR.
CONTINUOUS I.V. DRIP (C.T. 7 30 MIN.)
DAYS - 1 2 3 4 5 6 7 8 9 10 11 12 13 14

Fig. 2.—First method of penicillin therapy employed.

approximately 200,000 units daily. We are now using 17,000 units intramuscularly every two hours day and night. These patients received transfusions whenever their hemoglobin levels indicated the need for blood.

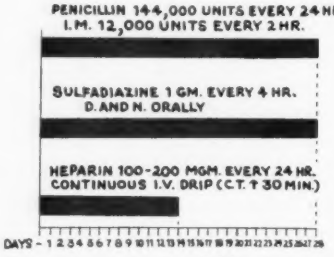
PENICILLIN 144,000 UNITS EVERY 24 HR.
I.M. 12,000 UNITS EVERY 2 HR.
SULFADIAZINE 1 GM. EVERY 4 HR.
D. AND N. ORALLY
HEPARIN 100-200 MGM. EVERY 24 HR.
CONTINUOUS I.V. DRIP (C.T. 7 30 MIN.)

Fig. 3.—Second method of penicillin therapy employed.

Figure 4 shows an example of the record made for each patient. The amount and the time of administration of penicillin and heparin were recorded. Lee and White clotting times were determined at 8 a. m., 3 p. m. and 10 p. m. every day. Daily urinalysis and blood cultures were made, along with complete blood counts, three times a week. Accurate measurements of the patient's urinary intake and output were made daily. Any reactions which occurred were fully described on these charts.

All of our patients with endocarditis presented a history and had physical findings on auscultation of the heart compatible with either rheumatic or congenital heart disease. All had been febrile for three

weeks or longer before treatment was instituted. All had definite evidence of embolization, and 10 of the 11 had splenomegaly. Ten had repeatedly positive blood cultures for alpha streptococci, and 1 had repeatedly positive blood cultures of beta hemolytic streptococci. Summaries of our cases are presented in table 3.

Of our 11 cases, in 3 the result was a definite failure. The time intervals since completion of treatment in our 7 cases of probable cures in which the patients are living are: 1 case, eighteen months; 3 cases, twelve months; and 3 cases, eleven months. The remaining patient died on the last day of combined penicillin-heparin treatment. She had no evidence of active endocarditis, and it is possible that heparinization was a primary cause of death. Although this patient died, she was free of all evidence of active endocarditis at postmortem examination, and the cultures obtained at autopsy from the blood and the

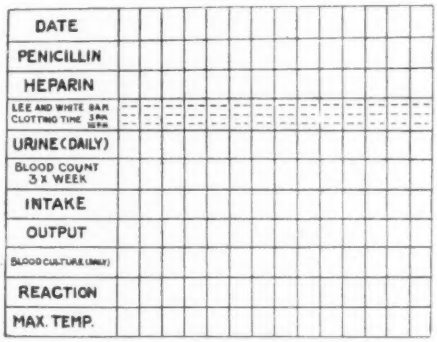


Fig. 4.—Example of record followed for each patient.

heart valve were negative. Of the 11 patients, 7 are probably cured and are living, and 1 was rendered free of endocarditis but died as a result of cerebral hemorrhage. Two additional patients whose cultures were not positive have been rendered afebrile and asymptomatic since completion of their treatment.

### DATA OBTAINED AT AUTOPSY IN AUTHORS' CASES

Case 1 (A. G.).—Postmortem examination revealed chronic rheumatic mitral valvulitis with no definite vegetations (fig. 5), renal and splenic infarcts and cerebral hemorrhage (fig. 6) involving the left frontal and parietal lobes and originating from the left middle cerebral vessels. Heparinization may have played a primary role in this patient's death. No evidence of active subacute bacterial endocarditis was present at postmortem examination.

Case 3 (C. M.).—Postmortem examination, performed by Dr. Pliny Allen, revealed moderate dilatation of all chambers of the heart, which was, however, maximal in the left auricle and ventricle. The myocardium was slightly soft

TABLE 3.—*Results of Treatment in Authors' Cases*

| Patient | Race | Sex | Age, Yr. | Duration of Symptoms Prior to Rx | Etiology of Heart Disease | Valves Affected | Blood Cultures | Penicillin Route, Amount/24 Hr., Duration Rx | Heparin: Days Used; Reactions | Sulfadiazine, Amount and Duration of Rx | No. of Courses of Penicillin and Heparin and Sulfadiazine | Results and Months Since Completion of Treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. A. G. | W | F | 22 | 4½ wk. | Rheumatic | Mitral | Alpha strep. | 200,000 units per 24 hr. I.V.; 13 days | 13 days; 4 reactions | None during penicillin Rx | 1 | Died (figs. 5, 6). Cerebral hemorrhage; no evidence of subacute bacterial endocarditis |
| 2. L. R. | W | M | 47 | 4 wk. | Rheumatic | Mitral, aortic | B. hemolytic strep. | 200,000 units per 24 hr. I.V.; 14 days | 10 days; no reactions | None during penicillin Rx | 2 | Cure, 18 mo.; afebrile, asymptomatic |
| 3. C. M. | C | M | 27 | 8 wk. | Rheumatic | Mitral | Alpha strep. | 200,000 units per 24 hr. I.V.; 16 days | 14 days; 6 reactions | None during penicillin Rx | 3 | Died (figs. 7, 8). Uremia and congestive heart failure and subacute bacterial endocarditis |
| 4. B. A. | W | F | 18 | 7 wk. | Rheumatic | Mitral, aortic | Alpha strep. | 200,000 units per 24 hr. I.V.; 16 days | 9 days; 12 reactions (during 4 courses of Rx) | 1 Gm. every 4 hr. day and night | 4 | Died. Uremia and congestive heart failure and subacute bacterial endocarditis |
| 5. J. M. | C | F | 20 | 4 mo. | Rheumatic | Mitral | Alpha strep. | 200,000 units per 24 hr. I.V.; 17 days | 13 days; no reactions | None during penicillin Rx | 1 | Cure, 12 mo. Afebrile, asymptomatic |
| 6. E. Z. | C | F | 25 | 3 mo. | Rheumatic | Mitral | Alpha strep. | 144,000 units per 24 hr. I.M. (÷ doses every 2 hr.); 27 days | 16 days; no reactions | 1 Gm. every 4 hr. day and night | 1 | Died (figs. 9, 10). Congestive failure and subacute bacterial endocarditis |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 7. V. L. | W | F | 29 | 1 mo. | Rheumatic | Mitral, aortic | Alpha strep. | 200,000 units per 24 hr. I.V.; 13 days | 8 days; 8 reactions | None during penicillin Rx | 2 | Cure, 12 mo. Afebrile, asymptomatic |
| 8. A. R. | W | F | 24 | 4½ mo. | Rheumatic | Mitral | Alpha strep. | 200,000 units per 24 hr. I.M.; 2 wk.; 100,000 units per 24 hr. I.M.; 2 wk. | None used | 1 Gm. every 4 hr. day and night | 1 | Cure, 12 mo. Afebrile, asymptomatic |
| 9. L. R. | C | M | 19 | 3 wk. | Rheumatic | Mitral | Alpha strep. | 144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 28 days | 14 days; no reactions | 1 Gm. every 4 hr. day and night | 1 | Cure, 11 mo. Afebrile, asymptomatic |
| 10. I. L. | W | F | 24 | 6 mo. | Rheumatic | Mitral | Alpha strep. | 200,000 units per 24 hr. I.M.; (÷ doses every 3 hr.); 42 days | None | None | 1 | Cure,* 11 mo. Afebrile, asymptomatic |
| 11. E. C. | C | M | 23 | 4½ wk. | Congenital | Patent ductus arteriosus (fig. 11) | Alpha strep. | 144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 30 days | 14 days; 4 reactions | 1 Gm. every 4 hr. day and night | 1 | Cure, 11 mo. Afebrile, asymptomatic |
| 12. E. P. | C | F | 17 | 2 mo. | Poss. rheumatic | Pulmonary, mitral | Negative | 144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 27 days | 16 days; no reactions | 1 Gm. every 4 hr. day and night | 1 | Cure, 9 mo. |
| 13. D. P. | W | M | 37 | 2 mo. | Rheumatic | Aortic, mitral | Negative | 144,000 units per 24 hr. I.M.; (÷ doses every 2 hr.); 27 days | 17 days; 14 reactions | 1 Gm. every 4 hr. day and night | 1 | Cure,† 6 mo. |

* We have learned that this patient died 11 months after completion of treatment. However, her physician reported that no evidence of active subacute bacterial endocarditis was present.

† This patient has recently returned to the hospital and is apparently in the bacteria-free stage of subacute bacterial endocarditis.

and reddish brown. The endocardium of the right side of the heart was smooth and glistening, and the tricuspid and pulmonary valves were delicate and competent and showed nothing of note. The endocardium of the left auricle was slightly

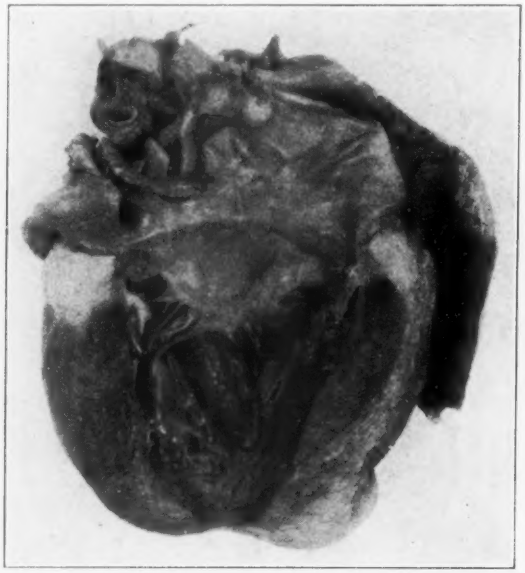

Fig. 5.—Chronic rheumatic mitral valvulitis in A. G. There were no definite vegetations.

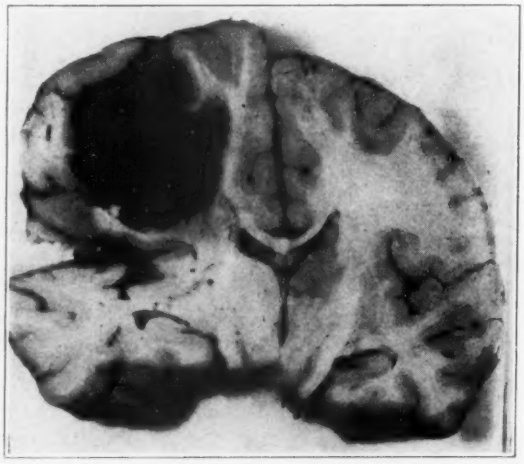

Fig. 6.—Cerebral hemorrhage involving the left frontal and parietal lobes (A. G.).

thickened and milky with a single oval patch measuring 2.5 by 2 cm. on the posterior wall just above the posterior leaflet of the mitral valve. The base of this patch was rough and red, and the patch was continuous with vegetations along the line of closure of the posterior leaflet of the mitral valve. These vegetations measured approximately 0.7 by 0.4 by 0.3 cm., and were firm and gray inferiorly, merging imperceptibly into the reddened, shaggy patch on the auricular wall superiorly. The anterior leaflet of the mitral valve was thickened moderately and showed a few vegetations. Some of the chordae tendineae were thickened, shortened and fused, especially those of the posterior leaflet. The aortic valve showed a slight degree of adherence at the commissures, and just beneath the commissures, between the posterior and left anterior cusps, was a single, soft, yellow vegetation, 0.1 cm. in diameter (fig. 7).

The final postmortem diagnosis was: (1) rheumatic heart disease with mitral and aortic valvulitis; (2) subacute bacterial endocarditis (Streptococcus viridans) involving the walls of the left auricle, mitral valve and aortic valve; (3) Strep.

Fig. 7.—Subacute bacterial endocarditis involving the walls of the left auricle of C. M.

viridans septicemia; (4) acute septic splenitis; (5) embolic glomerulonephritis with diffuse fibrous glomerulitis; (6) chronic passive congestion of the lung, spleen and liver; (7) pneumonia (rheumatic); (8) acute hepatitis; (9) portal cirrhosis of the liver (fig. 8); (10) ascites, and (11) chronic interstitial pancreatitis. Blood cultures and culture of the valve produced growth of Strep. viridans.

Case 4 (B. A.).—Postmortem examination revealed: (1) adhesive pericarditis; (2) rheumatic valvulitis (healed); (3) subacute bacterial endocarditis involving the mitral valve; (4) cardiac hypertrophy and dilatation; (5) infarctions of the spleen and kidney; (6) bronchopneumonia and (7) passive congestion of the intestine with hemorrhage into the mesentery of the small intestine.

Case 6 (E. Z.).—At postmortem examination the heart weighed 395 Gm. There were a few subepicardial petechiae. The chambers of both sides of the heart were considerably dilated. The valves of the right side of the heart and the

aortic valve showed nothing of note. The endocardium of the left auricle was slightly thickened, and over the posterior wall of the left auricle was a rounded patch measuring 5 by 4.5 cm., where the endocardium was completely covered by

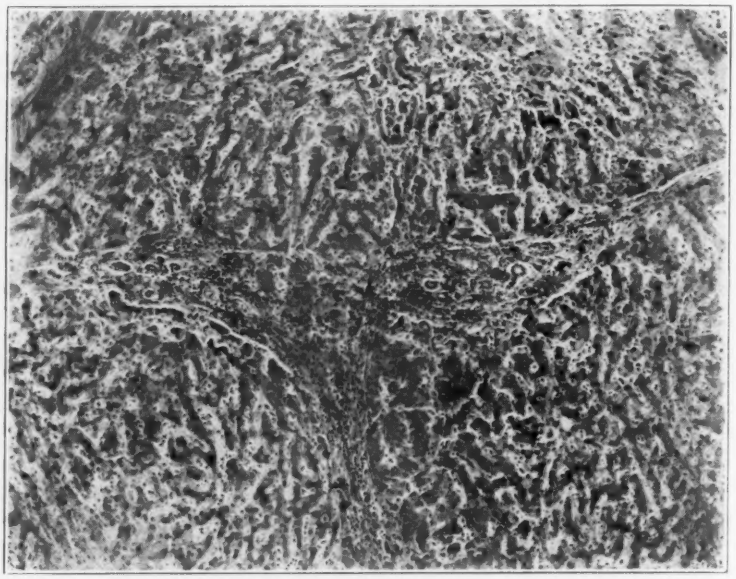

Fig. 8.—Portal cirrhosis (C. M.).

Fig. 9.—Subacute bacterial endocarditis involving the posterior wall of the left auricle and mitral valve of E. Z.

yellow-green, thick, soft, friable vegetations. The inferior edge of this patch extended onto the posterior leaflet of the mitral valve, involving it also in vegetations which extended down the chordae tendineae to the papillary muscles. Many

Fig. 10.—Mycotic aneurysm of the posterior medullary branch of the left middle cerebral artery of E. Z.

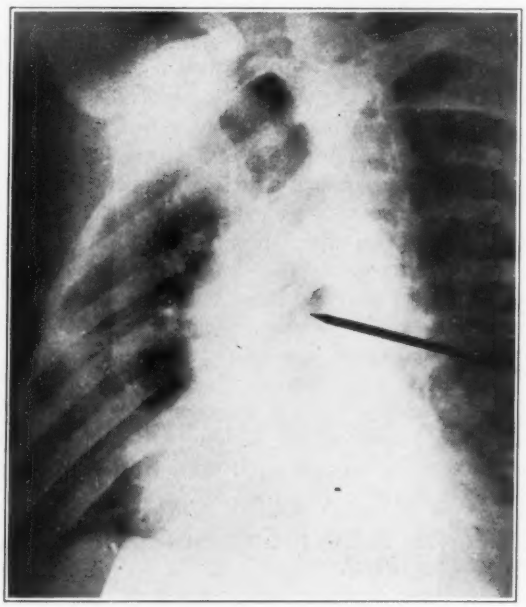

Fig. 11.—Injection of diodrast into patent ductus arteriosus of E. C.

chordae tendineae were thickened and fused, and one on the medial edge of the posterior leaflet of the mitral valve was ruptured at the junction with the valve at a site heavily involved in the vegetation. The entire line of closure of the valve showed numerous vegetations extending along the anterior and posterior leaflets (fig. 9).

The final postmortem diagnosis was: (1) rheumatic heart disease with mitral valvulitis, myocarditis and chronic pericarditis; (2) subacute bacterial endocarditis involving the posterior wall of the left auricle and mitral valve; (3) interstitial pneumonia; (4) cardiac dilatation and hypertrophy; (5) right hydrothorax; (6) hydropericardium; (7) ascites; (8) chronic passive congestion; (9) fatty metamorphosis of the liver; (10) multiple infarcts of the spleen, lungs and kidneys; (11) embolic glomerulonephritis; (12) cerebral embolus infarction; (13) generalized petechial hemorrhages and (14) mycotic aneurysm of the posterior medullary branch of the left middle cerebral artery (fig. 10).

Blood cultures at autopsy and culture from the heart valve yielded Strep. viridans.

## COMMENT

Theoretic considerations and autopsy observations in 1 of our fatal cases have caused us to form the opinion that heparinization favors fragmentation of the vegetations, leading to embolism, and that large cerebral hemorrhages are due to bleeding into infarcted areas as a result of diminished coagulability of the blood.

According to Allen,[41] the vegetations typically consist of three zones: The inner zone, which forms the bulk of the lesion, consists of a mass of fibrin and blood cells, in which varying degrees of necrosis occur. Allen found strands and bits of elastic and collagenous fibers in this zone, and believes it is derived from an exudative and destructive lesion of the cusp. The middle zone, of varying thickness, is composed of bacteria. The outer zone, usually only a fraction of a millimeter thick, consists of a layer of fibrin derived from the blood stream.

The vegetation, unlike ordinary thrombi, grows by propagation of the inner zones, not of the thin outer layer. Emboli probably break off owing to fragmentation which begins in the inner, necrotic zone. Heparinization would not induce such fragmentation, but might prevent reformation of the outer fibrinous layer at the site of rupture and thus allow continued breakdown of the vegetation, even to the point of complete disintegration, which is what apparently happened in 1 of our cases.

The dangers attendant on the employment of heparin are the possible initiation of embolism, the bleeding which may occur around the infarcted areas owing to prolonged clotting time of the blood and reactions due to sensitivity to heparin. McLean and others[42] also con-

41. Allen, A. C.: The Nature of the Vegetations of Bacterial Endocarditis, Arch. Path. **27**:661 (April) 1939.

42. McLean, J.; Meyer, B. B. M., and Griffith, J. M.: Heparin in Subacute Bacterial Endocarditis, J. A. M. A. **117**:1870 (Nov. 29) 1941.

sider the possibility of embolization being induced by the mechanical factors produced when excessive fluidity of the blood is caused by intravenous administration of heparin.

At present we advise heparinization only in those cases in which the disease has failed to undergo remission with one course of penicillin therapy. In such a case we would hope that heparinization might cause disintegration of the vegetations, and pray that the fragments will not enter the cerebral vessels.

The final evaluation of the part heparin will play in the treatment of subacute bacterial endocarditis will not be made until comparable series of large numbers of cases with and without the use of heparin are reported.

The results with penicillin therapy indicate the first real advance that has been made toward the conquering of a disease which previously had a mortality close to 100 per cent. Penicillin is by far the most effective agent we have for the treatment of subacute bacterial endocarditis. From the results available, it appears that endocarditis, in common with empyema and pneumococcus meningitis, will require prolonged administration of large doses of penicillin. At least 200,000 units a day for one month seems to be the optimal minimal dose in most cases. This dose should be increased if prompt remission is not induced. An occasional patient, as we demonstrated, succeeded in maintaining complete recovery after completion of two weeks of penicillin therapy. At present we believe that intramuscular administration at two hour intervals is the route of choice when therapy is to be continued so long.

Although various factors play a part in determining the final outcome of penicillin therapy, two main features determine its efficiency. The first factor is the extent of accessibility of the bacteriostatic and bactericidal action [43] of penicillin to the offending streptococci. This is determined in part by the size of the vegetation and the amount of fibrin and platelet barrier which is present on the vegetation. This in turn is dependent on the duration of the disease, those cases of over a few months' duration presenting more difficult opposition to the penetration of the vegetation by penicillin. The longer the endocarditis has been present, the more likely will be the possibility of permanent cardiac and renal damage. Even if the patient should recover from a long-standing endocarditis, his cardiac and renal status may be of such a low reserve as completely to incapacitate him or cause death. These are the reasons for the necessity of early diagnosis and early institution of treatment with adequate amounts of penicillin continued for a satisfactory interval.

43. Hobby, G. L.; Meyer, K., and Chaffee, E.: Observations on the Mechanism of Action of Penicillin, Proc. Soc. Exper. Biol. & Med. **50**:281, 1942.

After a patient recovers from an episode of subacute bacterial endocarditis, he should have a careful follow-up study and should be seen at least once every month for the first year. Foci of infection should be thoroughly investigated. Diseased tonsils, abscessed teeth and any other source of introduction of organisms into the blood stream should be eradicated. We advise that any dental or operative procedure be preceded and followed by the use of penicillin, as suggested by numerous authors.[44] It is well to keep in mind that minor manipulations of the teeth and gums may cause bacteremia. Okell and Elliott [45] found transient bacteremia following dental extractions in 75 per cent of patients with septic mouths, and in 34 per cent of patients without obvious dental infections.

## SUMMARY

1. The recent literature on the therapy of subacute bacterial endocarditis is briefly summarized.

2. We have presented our method of treatment of subacute bacterial endocarditis. The value of heparin, its mode of administration and reactions to it are discussed. Details of administration of penicillin and our views on the combination of penicillin with heparin and sulfadiazine have been discussed.

3. Nine cases in which the patients were treated with penicillin, heparin and sulfadiazine, and 2 in which they were treated with penicillin alone are summarized. Of our 11 patients, 7 are considered probably cured; 1 died from a heparin reaction, although she was free of all evidence of endocarditis at postmortem examination; and 3 failed to recover. Two additional cases with negative cultures, in which subacute bacterial endocarditis was successfully treated with penicillin, heparin and sulfadiazine are presented.

Dr. Edgar Hull rendered invaluable aid in carrying out this project and made many helpful suggestions, and Dr. Albert Lauve assisted us.

44. Budnitz, E.; Nizel, A. E., and Berg, L.: Prophylactic Use of Sulfapyridine in Patients Susceptible to Subacute Bacterial Endocarditis Following Dental Surgical Procedures: Preliminary Report, J. Am. Dent. A. **29**:346, 1942. Northrop, P. M., and Crowley, M. C.: The Prophylactic Use of Sulfathiazole in Transient Bacteriemia Following Extraction of Teeth: A Preliminary Report, J. Oral Surg. **1**:19, 1943; Further Studies on the Effect of the Prophylactic Use of Sulfathiazole and Sulfamerazine on Bacteremia Following Extraction of Teeth, ibid. **2**:134, 1944. Schwartz, S. P., and Salman, I.: The Effects of Oral Surgery on the Course of Patients with Diseases of the Heart, Am. J. Orthodontics **28**:331, 1942.

45. Okell, C. C., and Elliott, S. D.: Bacteriemia and Oral Sepsis with Special Reference to the Etiology of Subacute Endocarditis, Lancet **2**:869, 1935.

# STUDIES ON HYPERTENSION

## VI. Effect of Lowering the Blood Pressures of Hypertensive Patients by High Spinal Anesthesia on the Renal Function as Measured by Inulin and Diodrast Clearances

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THE common therapeutic practice of attempting to lower the blood pressure of hypertensive patients makes it wise to determine whether such lowering of blood pressure may have any adverse influence. In view of the relationship of arterial pressure to renal filtration, the frequency with which hypertensive states are associated with pathologic glomerular changes and the associated abnormalities which might influence arteriolar renal blood flow, it seemed especially desirable to determine whether therapeutically induced significant falls in blood pressure would affect renal function.

This problem has been previously investigated by the urea clearance as the criterion of renal function. It was found [1] that there was a decrease in urea clearance during the period that the blood pressure of hypertensive patients was decreased by spinal anesthesia. In view of the admitted defects of urea clearance as a method of determining renal function, we have reinvestigated the problem with the more precise methods of inulin and diodrast clearances.

### METHODS

Spinal anesthesia was induced by methods previously described.[2] Inulin clearances were studied with the one dose method of Alving and Miller,[3] and diodrast

From the Department of Internal Medicine, University of Texas School of Medicine and the John Sealy Hospital, Galveston, Texas.

1. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: I. The Effect on the Renal Function of Decreasing the Blood Pressure of Patients with Hypertension, Texas Rep. Biol. & Med. **1**:59-76, 1943.

2. Gregory, R.; Lindley, E. L., and Levine, H.: Studies on Hypertension: II. The Effect of Spinal Anesthesia on the Blood Pressure of Hypertensive Patients; Its Possible Bearing on the Pathogenesis of Essential Hypertension, Texas Rep. Biol. & Med. **1**:167-206, 1943; footnote 1.

3. Alving, A. S., and Miller, B. F.: A Practical Method for the Measurement of Glomerular Filtration Rate (Inulin Clearance), Arch. Int. Med. **66**:306-318 (Aug.) 1940.

clearances were determined according to the method of Goldring and Chasis.[4] The chemical determinations for inulin were made by Harrison's [5] modification of Alving, Rubin and Miller's method,[6] and the chemical estimations of diodrast were made according to the procedure employed by Alving, Flox and Pitesky.[7] Control clearance periods were run, and experimental clearance periods were run on a subsequent day—usually within three days after the control periods. Clearance periods were of approximately one hour's duration. It should be emphasized that the second hour of the experimental clearance periods served as a further control period, inasmuch as the blood pressure usually had risen to or toward the original levels.

## RESULTS

Table 1 shows values for inulin and diodrast clearance and filtration fractions obtained from the study of 4 patients with normal blood pressures. The results are within the accepted range of normal values for inulin.[7] Although the values obtained for diodrast clearances are

TABLE 1.—*Inulin and Diodrast Clearances of Patients with Normal Blood Pressure*

| | | | Inulin Clearance | | Diodrast Clearance | | Filtration Fraction | | |
|---|---|---|---|---|---|---|---|---|---|
| Patient | Age | Blood Pressure | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | Diagnosis |
| P. P. | 37 | 124/86 | 99 | 76 | 479 | 407 | 0.207 | 0.186 | Nontoxic adenoma of thyroid gland |
| F. J. | 67 | 150/84 | 106 | .. | 336 | 332 | 0.312 | ..... | Chronic duodenal ulcer |
| B. B. | 53 | 130/68 | 83 | 76 | 312 | 314 | 0.266 | 0.242 | Infection of upper respiratory tract |
| M. S. | 50 | 116/70 | 100 | 77 | 449 | 444 | 0.223 | 0.175 | Pulmonary abscess |

somewhat less than those noted by Goldring and Chasis,[8] they conform to the normal figures given by White, Findley and Edwards [9] and Chesley and Chesley.[10]

4. Goldring, W., and Chasis, H.: Hypertension and Hypertensive Disease, New York, The Commonwealth Fund, 1944, p. 196.

5. Harrison, H. E.: A Modification of the Diphenylamine Method for Determination of Inulin, Proc. Soc. Exper. Biol. & Med. **49**:111-114, 1942.

6. Alving, A. S.; Rubin, J., and Miller, B. F.: A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, J. Biol. Chem. **127**:609-616, 1939.

7. Flox, J.; Pitesky, I., and Alving, A. S.: A Direct Photoelectric Colorimetric Method for the Determination of Diodrast and Iodides in Blood and Urine, J. Biol. Chem. **142**:147-157, 1942.

8. Goldring and Chasis,[4] p. 56.

9. White, H. L.; Findley, T., Jr., and Edwards, J. C.: Interpretation of Diodrast Clearances in Man, Proc. Soc. Exper. Biol. & Med. **43**:11-14, 1940.

10. Chesley, L. C., and Chesley, E.: The Diodrast Clearances and Renal Blood Flow in Normal Pregnant and Non-Pregnant Women, Am. J. Physiol. **127**:731-737, 1939.

Table 2 contains values for inulin and diodrast clearances of 12 patients with hypertension selected at random before, during and immediately following the effects of high spinal anesthesia. Ten of these patients had received clinical diagnoses of essential hypertension. Two of them (L. F. and H. B.) undoubtedly had chronic glomerulonephritis, as our records showed they had passed through a nephrotic stage prior to the chronic stages. Four of the 12 (C. B., D. S., W. L. and H. B.) had nonprotein nitrogen values of 121 to 381, 78, 45 and 79 mg. per hundred cubic centimeters, respectively. None of the patients had cardiac failure as decided by clinical means or by normal venous pressures and circulation times in most cases. Only 1 patient (E. P.) failed to show a fall in pressure. The remaining 11 had falls of systolic pressure of from 40 to 140 mm. of mercury and of diastolic pressure of from 20 to 80 mm. Seven of them (E. G., E. R., C. B., M. L., F. H., M. D. and W. L.) had falls to normotensive levels for thirty-six to one hundred and twenty minutes. One (L. F.) experienced a fall of blood pressure to normotensive levels for only five minutes. One patient (D. S.) had a significant fall of pressure from 230 systolic and 146 diastolic to a low of 180 systolic and 110 diastolic, with a continuation of a significant fall for ninety-six minutes. G. M. had a fall from 252 systolic and 130 diastolic to a low of 164 systolic and 110 diastolic; a significant fall of blood pressure was maintained, however, for only twenty minutes. The blood pressure of H. B. fell from 236 systolic and 150 diastolic to a low of 170 systolic and 90 diastolic; but the significant fall persisted for only fifteen minutes.

Further analysis of the data in table 2 demonstrates that a significant fall in inulin and diodrast clearances occurred in every instance in which the blood pressure fell significantly for as long as fifteen minutes. It can also be seen that the degree of decrease in the inulin and diodrast clearance is roughly proportional to the amount and duration of the fall in blood pressure.

That the decrease in clearance values is probably caused by the drop in blood pressure is evidenced by the following data: 1. The clearance values invariably rose to or toward the control levels during the second experimental hour, when the blood pressure had risen to or toward control levels. 2. In several patients, exemplified by M. D., in whom the blood pressure remained low for two hours, the inulin and diodrast clearances remained proportionally low. 3. In 1 patient (E. P.), in whom there was no fall in blood pressure but a slight unexplained rise and in whom sensory paralysis had reached the second interspace and there was complete motor paralysis of the lower extremities, there was no decrease in clearance values but a definite increase in these clearances.

TABLE 2.—*Effect on Inulin and Diodrast Clearances of Lowering Blood Pressures of Patients with Hypertension by Means of High Spinal Anesthesia*

| Patient | Blood Pressure | | Duration of Significant Lowering, Min. | Sensory Level | Inulin Clearance | | | | | | Diodrast Clearance | | | | | | Filtration Fraction | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Control | | Experimental | | % Change | | Control | | Experimental | | % Change | | Control | | Experimental | |
| | Initial | Lowest | | | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour | First Hour | Second Hour |
| E. G. | 230/122 | 108/ 72 | 120 | 3d I. S. | 66 | 56 | 40 | 87 | −25 | +18 | 208 | 212 | 102 | 102 | −81 | −59 | 0.317 | 0.264 | 0.392 | 0.85 |
| E. R. | 220/128 | 102/ 72 | 56 | 2d I. S. | 84 | 71 | 50 | 124 | −40 | +75 | 295 | 270 | 234 | 254 | −21 | − 6 | 0.285 | 0.263 | 0.213 | 0.488 |
| C. B.* | 228/140 | 110/ 80 | 85 | 3d rib | 10 | 8 | 3 | 7 | −72 | −15 | 27 | 29 | 5 | 14 | −82 | −50 | 0.37 | 0.276 | 0.557 | 0.472 |
| M. L. | 270/170 | 130/ 90 | 66 | 2d I. S. | .. | 143 | 112 | 126 | −22 | −12 | .. | 645 | 472 | 771 | −27 | +20 | ..... | 0.222 | 0.237 | 0.164 |
| D. S.† | 230/146 | 180/110 | 96 | 4th I. S. | 48 | 43 | 39 | 49 | −19 | −14 | 119 | 119 | 102 | 125 | −14 | + 5 | 0.406 | 0.361 | 0.382 | 0.392 |
| F. H. | 150/ 90 | 110/ 70 | 46 | 3d rib | 93 | 82 | 77 | 89 | −17 | + 9 | 452 | 382 | 283 | 344 | −37 | −10 | 0.206 | 0.214 | 0.272 | 0.258 |
| M. D. | 190/100 | 120/ 70 | 36 | 2d I. S. | 98 | 116 | 73 | 83 | −26 | −28 | 475 | 486 | 357 | 357 | −25 | −27 | 0.206 | 0.238 | 0.204 | 0.231 |
| G. M. | 252/130 | 164/110 | 20 | 2d I. S. | 62 | 63 | 46 | 49 | −26 | −22 | 246 | 268 | 221 | 243 | −10 | − 9 | 0.252 | 0.235 | 0.208 | 0.202 |
| W. L.‡ | 180/120 | 120/ 76 | 84 | 3d I. S. | 41 | 37 | 8 | 32 | −81 | −14 | 136 | 130 | 27 | 169 | −81 | +30 | 0.301 | 0.285 | 0.297 | 0.189 |
| E. P. | 150/110 | No fall | Rose to 170/154 | 2d I. S. | 62 | 57 | 73 | 78 | +18 | +37 | 345 | 340 | 403 | 402 | +17 | +18 | 0.180 | 0.168 | 0.181 | 0.194 |
| L. F.(N) | 142/ 86 | 98/ 62 | 5 | Clavicle | 25 | 19 | 18 | 13 | −28 | −32 | 437 | 367 | 333 | 416 | −24 | +13 | 0.057 | 0.052 | 0.054 | 0.031 |
| H. B.(N)§ | 236/150 | 170/ 90 | 15 | Clavicle | 13 | 13 | 6 | 8 | −51 | −38 | 64 | 64 | 19 | 39 | −70 | −39 | 0.199 | 0.203 | 0.33 | 0.212 |

(N) Chronic nephritis.

* Nonprotein nitrogen 121-381 mg. per hundred cubic centimeters.

† Nonprotein nitrogen 78 mg. per hundred cubic centimeters.

‡ Nonprotein nitrogen 45 mg. per hundred cubic centimeters.

§ Nonprotein nitrogen 79 mg. per hundred cubic centimeters.

The filtration fraction is elevated in most patients with essential hypertension during even the early stages.[11] This is usually interpreted to be due to a selective increase in vasomotor tonus of the efferent glomerular arteriole.

The filtration fractions in this study were found to be high in 6 of 12 patients. Five patients had normal fractions, and 1 had a severely reduced filtration fraction. In the latter instance (L. F.) the filtration fraction was reduced to 0.05, about 25 per cent of the normal value. This patient (L. F.) had chronic glomerulonephritis, with a nephrotic syndrome and a greatly reduced filtration rate with a normal effective renal plasma flow. The other patient with nephritis (H. B.) had a normal filtration fraction.

Theoretically, one might expect that high filtration fractions associated with essential hypertension would fall under high spinal anesthesia if there is a selective increase in vasomotor tone to the efferent glomerular arteriole. Analysis of our filtration fractions yielded no uniform trend. Of the 6 patients (E. G., E. R., C. B., D. S., G. M. and W. L.) who had a high filtration fraction, 2 (E. G. and C. B.) showed a significant (more than 0.02) rise in filtration fraction, 2 (E. R. and G. M.) had a significant fall and 2 (D. S. and W. L.) showed no significant change in filtration fraction during high spinal anesthesia and associated significant falls of blood pressures.

We are unable to explain the lack of uniformity in the effect of spinal anesthesia on filtration fractions. It may be explained by the variability of several factors, such as the drop in blood pressure, different degrees of organic change in the afferent or efferent arterioles and differences in the amount of glomerular damage.

Certain other pertinent features of this study have been graphically presented in charts 1, 2 and 3. Chart 1 summarizes the results on patient F. H., who had normal inulin and diodrast clearances. The blood pressure fell under spinal anesthesia to normotensive levels for approximately forty-five minutes. During the first hour's observation the inulin and diodrast clearances fell significantly. During the second hour of the experimental period the blood pressure returned to its original hypertensive levels. During this hour the inulin clearance returned to the control level and the diodrast clearance moved toward but did not attain control levels.

Chart 2 illustrates the results on M. D., who had normal renal clearance values. High spinal anesthesia, however, caused a great fall in blood pressure for the entire hour of the first clearance period and for more than half of the second clearance period. There was a significant

11. Goldring and Chasis,[4] p. 61.

decrease in inulin and diodrast clearances during the first period. These values remained essentially the same during the second clearance period because of the persistence of the fall in blood pressure well into the second clearance period.

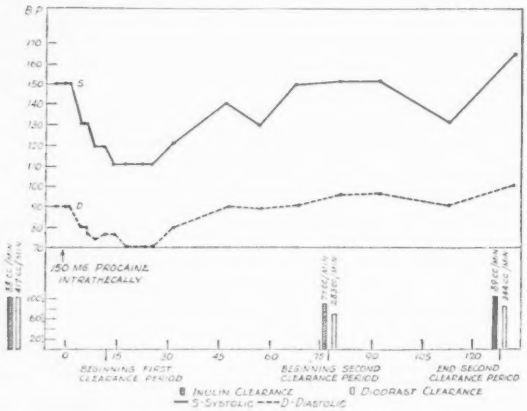


Chart 1 (patient F. H.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in patient with normal inulin and diodrast clearances.

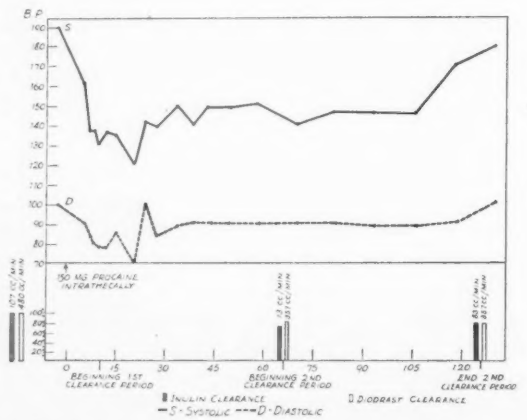


Chart 2 (patient M. D.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in patient with normal renal clearance values.

Chart 3 graphically presents the data obtained from the study of W. L. This patient had great impairment of renal function, shown by low clearance values. During high spinal anesthesia the fall in blood pressure was great and the pressure remained at normotensive levels

during all of the first clearance period. Concurrently with this intensive drop in blood pressure, there was extreme depression of inulin and diodrast clearances. During the second clearance period the blood pressure rose rapidly toward the original level after the first twenty minutes of this period. The inulin clearances rose to the control level, and the diodrast clearance exceeded the control level during this period.

These figures graphically emphasize features which are shown in table 2, namely, that in hypertensive patients there is a close correlation between falls in blood pressure induced by high spinal anesthesia and inulin and diodrast clearances. This correlation occurs in patients with either normal or impaired renal function.

It is realized that the duration of the falls in blood pressure and the concomitant decreases in inulin and diodrast clearances are for short

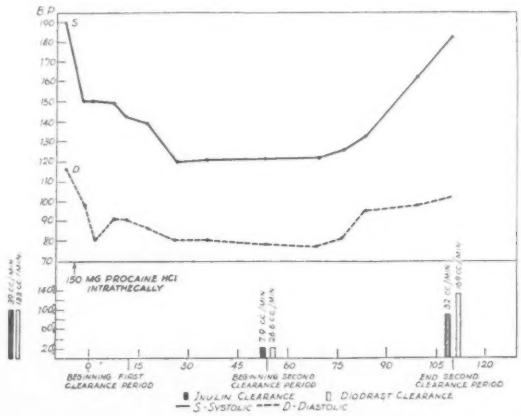


Chart 3 (patient W. L.).—Pattern of systolic and diastolic pressures during high spinal anesthesia in a patient with considerable impairment of renal function.

periods. The results of this study emphasize the necessity, however, for the study by precise methods of the effect on renal function of any therapeutic regimen which symptomatically lowers the blood pressure.

## SUMMARY

The effect of lowering the blood pressure on renal function has been studied by inulin and diodrast clearances in 10 patients with essential hypertension and in 2 patients with chronic glomerulonephritis. The data have been presented in two tables and three graphs.

## CONCLUSION

Fall in blood pressure induced by high spinal anesthesia to no lower than normotensive levels were associated with a decrease in inulin and

diodrast clearances in 10 patients with essential hypertension and in 2 patients who had chronic glomerulonephritis.

It is believed that the fall in blood pressure is etiologically related to the decrease in renal function.

The decrease in renal function with the fall in blood pressure occurs in patients who have either normal or impaired renal function.

The results of this study necessitate a critical appraisal of the effect on renal function of any therapeutic effort which aims at symptomatic lowering of the blood pressure in patients with hypertension.

# A ROENTGEN RAY AND CLINICAL STUDY OF PRIMARY TUBERCULOSIS

## Vollmer Patch Test Made on Four Hundred and Sixty Patients; Positive Reactions Secured in One Hundred and Fifteen

ALFRED D. BIGGS, M.D.

With the Technical Assistance of Miss Irene Stolp, R.N.

CHICAGO

THERE is no uniformity of opinion concerning the fundamental biologic responses invoked in the human body when tubercle bacilli are introduced into it.

### ALLERGY

There is abundant evidence that an allergic response is set up in the tissues of experimental animals by the introduction of tubercle bacilli. The first dose of tubercle bacilli injected into the skin of a guinea pig does not cause hyperemia. After sensitization the same dose will cause hyperemia. Long [1] has shown that a small dose of tubercle bacilli injected into the testis of a normal guinea pig has no immediate effect. However, if the animal has been previously sensitized, the same number of bacilli cause rapid degeneration of the testicle. It has been shown that leukocytes from normal animals are not harmed by contact with tuberculin, whereas leukocytes from tuberculous animals are damaged by similar contact.

Aronson [2] has shown that the growth of cultures of tissue from tuberculous guinea pigs is inhibited and their cells damaged by contact with tuberculin, whereas similar cultures from normal pigs are not thus affected by contact with tuberculin.

If tuberculoprotein is placed in the conjunctival sac of a sensitized guinea pig the destruction may be great enough to destroy vision. These and other evidences of the allergic response are summarized by Myers [3] in his monograph. This sensitizing process is said to vary with different species.

1. Long, E. R.: Tuberculous Reinfection and Tuberculin Reaction in Testicle of Tuberculous Guinea Pig, Am. Rev. Tuberc. **9**:215-253 (May) 1924.

2. Aronson, J. D.; Zacks, D., and Poutas, J. J.: Comparative Sensitiveness of Pirquet and Intracutaneous Tuberculin Tests, Am. Rev. Tuberc. **27**:465-473 (May) 1933. Aronson, J. D.: The Purified Protein Derivative, with Special Reference to Technique of Tuberculin Injections and Grading of Reactions, ibid. **30**:727-732 (Dec.) 1934.

3. Myers, J. A., and others: Tuberculosis among Children and Young Adults, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1938.

IMMUNITY

Although it cannot be clearly demonstrated in the laboratory, there is a general belief that tubercle bacilli evoke some sort of immunologic process in the experimental animal and also in man. It has been shown that tubercle bacilli migrate more slowly from the point of injection to the internal structures in the sensitized animal than in the normal animal. Greater numbers of bacilli die out in the previously inoculated animal than in the normal animal. Koch [3] is said to have observed this phenomenon in part. Whether these two processes, i. e., allergy and immunity, exist as independent or as interdependent factors has not been determined.

In other parts of the globe millions of children have received injections of attenuated tubercle bacilli (BCG) with the idea of producing a protective immunity. There is no end of discussion about the value of this procedure.

The physician must decide which is the dominant one of these two factors in the spread and control of tuberculosis. Is it allergy, or is it immunity? Until recent years it has been an accepted belief that immunity is the dominant factor. The late eminent pathologist, H. G. Wells, used to say that the Lord's Prayer should be amended to read, "Give us this day our daily tubercle bacilli," thus emphasizing immunity to tuberculosis. On the other hand, in recent years Myers [3] and Stuart, who have devoted a great deal of time and energy to this problem, have presented much evidence, both laboratory and clinical, to indicate that allergy is the all-important factor in the spread and control of this disease. According to this conception, when tubercle bacilli are first introduced into the human body and produce the primary complex, this occurs uniformly without gross destruction of tissue and without discomfort to the host, in much the same way as the original introduction of ragweed pollen into the system occurs without symptoms.

Long and Seibert [4] have shown that the tubercle bacillus is composed of lipids, polysaccharides and an unstable water-soluble protein resembling albumin, and that sensitivity to tuberculin—and therefore the reaction to tuberculin tests—is due solely to this tuberculoprotein. The primary tuberculous infection sensitizes all the body tissues to tuberculoprotein; therefore, if a sufficient number of bacilli are introduced again into any part of the body an allergic response is invoked, char-

4. Long, E. R., and Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin, Am. Rev. Tuberc. **13**:393-453 (May) 1926. Seibert, F. B.: The Chemical Composition of the Active Principle of Tuberculin: Isolation in Crystalline Form and Identification of Active Principle of Tuberculin, ibid. **17**:402-421 (April) 1928.

acterized by gross destruction of tissue—lung, kidney, bone, lymph node or epididymis. The relative importance of allergy and immunity in tuberculosis is debatable.

### TUBERCULIN TESTS

Von Pirquet was the first to devise a tuberculin test which gained extensive recognition. He placed a little old tuberculin on the scarified skin. An indurated area appearing during the next forty-eight hours indicates sensitivity to tuberculoprotein. Later Mantoux modified the technic by injecting a small amount of old tuberculin intradermally. The Mantoux test detects a larger number of reactors and therefore is considered superior to the von Pirquet test.

Seibert and Glenn [5] further modified the intracutaneous technic. Using their tuberculoprotein, which they designated "purified protein derivative," they injected a freshly prepared solution containing 0.00002 mg. of tuberculoprotein. This minute quantity is known as first test strength of purified protein derivative, and a test with it will be referred to in this study as P. P. D. test 1. As in the Mantoux test, an indurated area of skin approximately 10 mm. or more in diameter appearing within forty-eight hours indicates sensitivity to tuberculoprotein and therefore to tuberculosis. If a person has a negative reaction to this test, he receives a second intracutaneous injection exactly two hundred and fifty times as great as the first. This amount is known as second test strength, and a test with it will be referred to in this study as P. P. D. test 2. If a person does not react to this test he is considered to be insensitive to tuberculin. In 1937, after years of investigation of tuberculosis by a committee on medical research of the National Tuberculosis Association, the managing director issued a statement indicating that purified protein derivative is distinctly superior to old tuberculin for intracutaneous tests. I therefore selected P. P. D. tests as a standard for testing the efficacy of the Vollmer patch test.[3]

Many attempts have been made to devise a satisfactory percutaneous test, or one in which the tuberculin is introduced into the deeper layers of the skin without the use of the needle. Tuberculin ointments proved unsatisfactory. Of the numerous patch tests, the one devised by Vollmer and Goldberger [6] and commercially prepared by Lederle Laboratories, Inc., appears to be the simplest and the most efficient. It consists of two pieces of absorbent material 1 cm. square which have

5. Seibert, F. B., and Glenn, J. T.: Tuberculin Purified Protein Derivative: Preparation and Analyses of a large Quantity for Standard, Am. Rev. Tuberc. **44**:9-25 (July) 1941. Seibert, F. B.: The Isolation and Properties of Purified Protein Derivative of Tuberculin, ibid. **30**:713-720 (Dec.) 1934.

6. Vollmer, H., and Goldberger, E. W.: New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019-1024 (Nov.) 1937.

previously been soaked in a suspension of old tuberculin and placed on an oblong strip of adhesive tape with a control piece between the two. After the skin has been thoroughly cleansed with acetone or ether to remove all fatty material, the patch is applied. It is removed after forty-eight hours and read after an additional forty-eight hours. When positive, the reaction appears as a sharply defined indurated reddened square, with lichenoid follicular elevations of the skin. If the reaction is strongly positive, there may be considerable induration of the skin spreading beyond the limits of the patch, followed by scaling and temporary pigmentation.

Vollmer and Goldberger first reported this technic in 1937 and stated that it was more sensitive than the von Pirquet test, with which they had compared it. Most experimenters agree with this statement. In subsequent reports,[7] using a stronger patch, Vollmer and Goldberger compared it with the P. P. D. tests and also with the Mantoux test with 0.1 mg. of old tuberculin. They reported almost 100 per cent agreement with these tests. The reports of other workers have been a little less favorable. In a series of 257 cases, Weiner and Neustadt[8] reported 95 per cent of the patients with positive reactions to the Mantoux also had positive reactions to the Vollmer Patch test. Hart[9] reported that patch tests detected 97 out of 100 Mantoux reactors. He used both the Vollmer patch and the Copenhagen patch. Court[10] reported 98 per cent agreement in 110 cases. Fineman and Bair[11] reported 97 per cent agreement in 330 cases. In both instances the Vollmer test was less sensitive than the Mantoux. Peck and Wegman[12] reported only 30 per cent agreement with the P.P.D. tests. This report is distinctly out of line with the others.

The purpose of this study is twofold: (1) to compare the sensitivity of the Vollmer patch with the purified protein derivative tests; and (2)—and this I regard as the more important—to make, record and correlate the clinical and roentgenologic observations on all positive reactors

7. Vollmer, H., and Goldberger, E. W.: Comparative Study of Tuberculin Patch Test and Mantoux Intracutaneous Test, Am. J. Dis. Child. **56**:584-586 (Sept.) 1938; Evaluation of the Tuberculin Patch Test (Vollmer-Lederle), ibid. **57**:1272-1277 (June) 1939.

8. Weiner, S. B., and Neustadt, A.: Tuberculin Patch Test: Comparison with Pirquet and Mantoux Tests, J. Pediat. **14**:752-754 (June) 1939.

9. Hart, F. D.: Tuberculin Patch Test in Children, Lancet **2**:609-610 (Sept. 10) 1938.

10. Court, S. D. M.: Comparative Study of Tuberculin "Patch Test" and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. **1**:824-825 (April 22) 1939.

11. Fineman, A. H., and Bair, G.: Evaluation of Tuberculin Patch Test, Am. J. Dis. Child. **60**:631-634 (Sept.) 1940.

12. Peck, E. C., and Wegman, M. E.: Comparison of the Vollmer Tuberculin Patch Test with Purified Protein Derivative, J. Pediat. **15**:219-223 (Aug.) 1939.

over a long period. This should be valuable in appraising the relative importance of allergy and immunity in tuberculosis.

## PROCEDURE

In the outpatient department of St. Luke's Hospital prior to 1941, my colleagues and I performed tuberculin tests on known contacts and on a few other children. During 1941 and 1942 every child over 1 year of age was tested with tuberculin as a matter of routine. On the appointed day, first test strength purified protein derivative was injected and the Vollmer patch applied. Two days later the child returned and the P. P. D. test 1 was read and the patch removed. In the event that P. P. D. test 1 elicited a negative or doubtful reaction second test strength P. P. D. test was given. The child again returned after two more days for reading of the patch and of P. P. D. test 2. If the results of the two tests did not agree or if the results were doubtful, the entire procedure was repeated as a check. To the 1941 and 1942 group were added those tested in previous years.

Therefore, this study does not indicate the percentage of reactors in our dispensary population. Every child tested is included in the summary except those who failed to go through with all the tests. The tests were completed on 460 children.

Of the total, exactly one fourth, or 115, reacted to at least one of the tests. These 115 were studied routinely as follows: They were questioned very carefully and diligently concerning exposure to tuberculosis. These children were brought back regularly every third or sixth month and in many cases oftener. At each visit they were weighed and measured, temperatures were taken, and physical examinations, including examinations of the chest, were made. Serial roentgenograms of the chest were made at regular intervals, usually once a year. Many chests were again given roentgenologic examination after two, three, four or six months, at the suggestion of the roentgenologist. These were cases that appeared to be changing more rapidly than others. More than half of these children have been under observation for five years; many of them ten years or longer.

Since all tuberculin tests are based on an allergic phenomenon, it follows necessarily that none is infallible. The possibility of false negative reactions and false positive reactions must always be borne in mind. For this reason it was considered necessary to keep each positive reactor under close clinical observation and to study him with serial roentgenograms.

The results of the observations on each of the 115 children with positive reactions to tuberculin were carefully tabulated and correlated. These observations include clinic identification number, race, sex, age, history of contact with communicable tuberculosis, results of tuberculin tests, observations from serial roentgenograms, red and white blood cell counts, estimations of hemoglobin, results of repeated examinations of

the chest and records of growth, weight and temperatures. The results of these studies are briefly set forth in the following paragraphs.

## RESULTS

*Racial Incidence.*—The conception that certain races are more susceptible to tuberculosis than others has been challenged by Myers.[3] He stated his belief that the higher incidence of tuberculosis among Negroes, Mexicans and North American Indians is due to their poorer living conditions. I placed the Negroes and Mexicans in one group and compared the incidence to that in the white group. Among 293 dark-

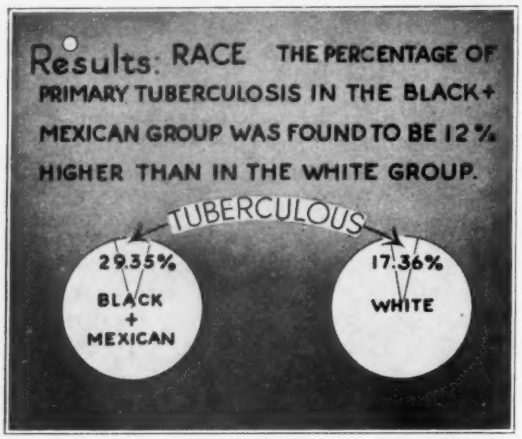


Figure 1.

skinned children, 86 had positive reactions to tuberculin and exhibited roentgenologic evidence of tuberculosis. In the white group, 29 out of a total of 167 gave the same evidence of primary tuberculosis. Thus the incidence of tuberculosis in the dark-skinned group was approximately 29 per cent as compared with 17 per cent in the white group (fig. 1). I believe that this difference of 12 per cent can be accounted for justly by the poorer living conditions of the former group.

*Tuberculin Tests.*—As stated earlier, 115 out of the whole group of 460 children reacted to at least one of the tuberculin tests. The Vollmer patch agreed with the purified protein derivative tests in 100 out of the 115 cases in which there was a reaction. Therefore the tests disagreed in 15 instances, or in 3 per cent of the entire series (fig. 2).

Of the 15 children concerning whom the Vollmer patch and the purified protein derivative tests did not agree, 14 had positive reactions to one of the purified protein derivative tests and negative reactions to

the Vollmer patch, whereas 1 child reacted to the patch and had an entirely negative reaction to both P. P. D. test 1 and P. P. D. test 2 (fig. 3). These facts indicate that neither test is infallible and also

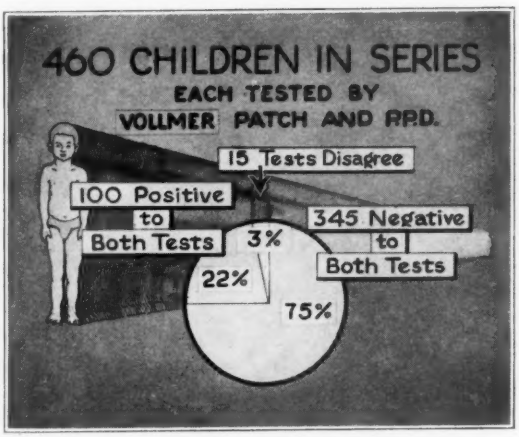


Figure 2.

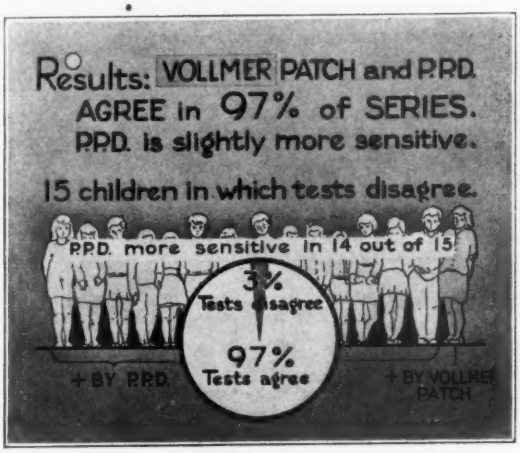


Figure 3.

that the Vollmer patch test is slightly less sensitive than the purified protein derivative tests.

*Serial Roentgenograms.*—Each of the 115 children whose reactions to tuberculin were positive has been examined at least once roentgeno-

logically. More than half of them have been examined by serial roentgenograms over a period of five years, and some over a period of ten years. The lesion of primary pulmonary tuberculosis appears first peripherally. The usual location is the first, second or third intercostal

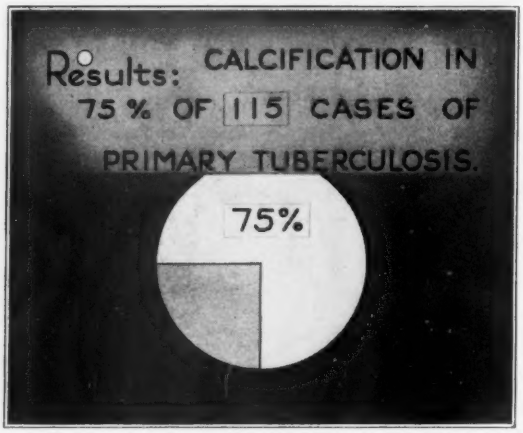


Figure 4.

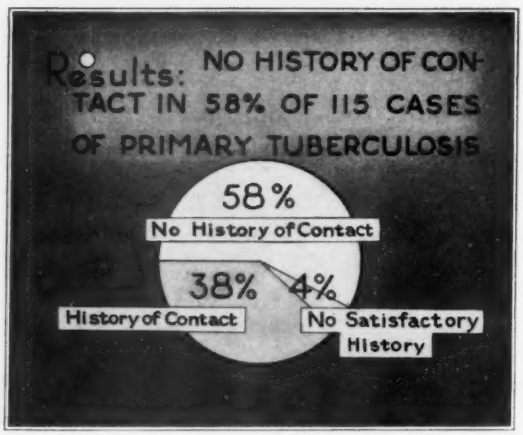


Figure 5.

space, on either the right or the left side. It is usually bilateral. It may also be in the apex. This initial lesion is rather ephemeral and rapidly hardens. At the same time the shadows of the hilar lymph nodes enlarge. In a typical case, these slowly calcify. The end results

are calcified hilar nodes and linear peripheral markings. In some instances the peripheral lesion calcifies enough to register a dense shadow. This is a Ghon tubercle. In the present series this occurrence is decidedly the exception and not the rule. Calcification of hili is the rule and has already occurred in 84 cases, or 75 per cent of the series (fig. 4).

The majority of the patients dealt with in the present study had calcified glands at the first examination. In 18 calcification began while they were under observation. The interval between the first roentgenogram showing tissue change and the roentgenogram showing the appearance of calcium shadows varied from a few months to three years.

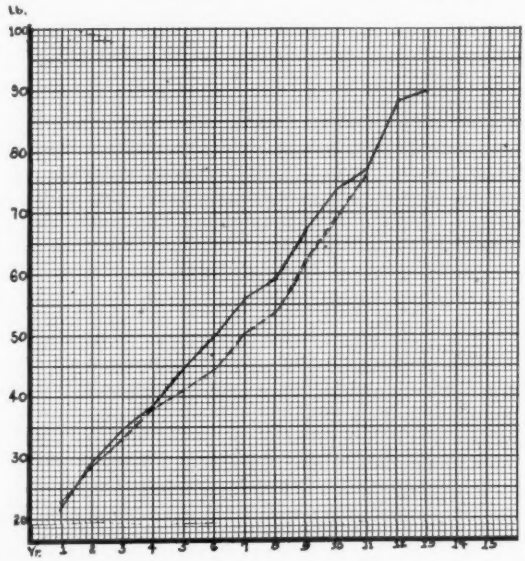


Fig. 6.—The solid line indicates the weights of boys whose reactions for tuberculosis are positive. The broken line indicates the weights of boys whose reactions are negative.

In the great majority of cases the lapse of time was between six months and two years. A very few remained without demonstrable calcification after three years. The roentgenograms in this series were read by Dr. E. L. Jenkinson and his associates.

There are no shadows specific for primary tuberculosis. The shadows caused by bronchitis or repeated respiratory infections are similar to those of primary tuberculosis. The roentgenologic observations must be correlated with the results of the test with tuberculin and the clinical history. In some instances a single roentgenogram is sufficient for this purpose; in others serial roentgenograms are necessary.

*Incidence of Contact.*—The history of each of the 115 patients was diligently explored and all clues followed. Yet a history of contact with communicable tuberculosis could be obtained in only 44 instances, or in 38 per cent of the series (fig. 5). Presumably the great majority of these children acquired the disease outside of their homes. This emphasizes the public health aspect of tuberculosis.

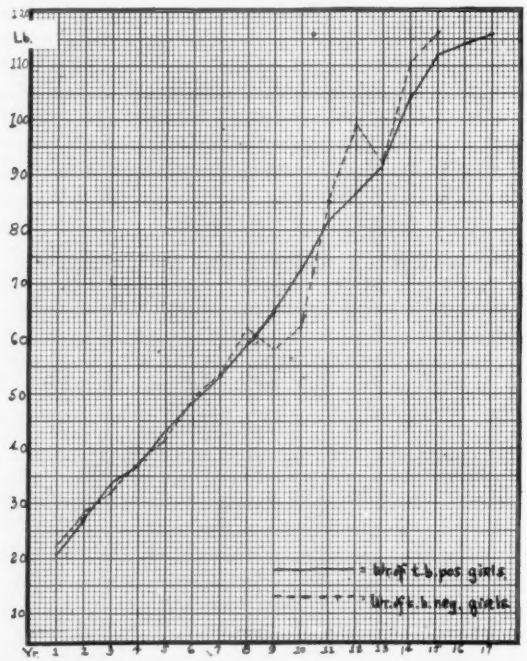


Fig. 7.—The solid line indicates the weights of girls whose reactions for tuberculosis are positive. The broken line indicates the weights of girls whose reactions are negative.

*Clinical Data.*—The general opinion among physicians appears to be that primary tuberculosis is a disease with mild clinical symptoms, such as a low grade fever with a generally poor state of health and perhaps some minimal physical signs in the chest. These opinions were not confirmed in this series, as the following data indicate:

*Fever.*—None of these children had a prolonged fever.

*Blood.*—Blood counts and estimations of hemoglobin were made for 110 of the 115 patients. The average red blood cell count was 4,100,000; the average white blood cell count, 7,500; the average hemoglobin content, 13.2 Gm. per hundred cubic centimeters (see the table).

Although there were no controls, these values are not significantly different from those of the average child encountered in the clinic.

*Gain in Weight.*—The boys and girls were divided into separate groups. The average gain in weight from 1 year of age until well into

*Blood Counts in 115 Cases of Primary Tuberculosis*

| These counts are not significantly different from those of the average clinic child | |
|---|---|
| Red cells | 4,100,000 |
| White cells | 7,500 |
| Hemoglobin | 13.2 Gm. |

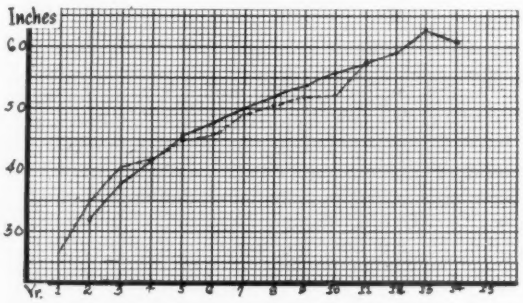


Fig. 8.—The solid line indicates the heights of boys whose reactions for tuberculosis are positive. The broken line indicates the heights of boys whose reactions are negative.

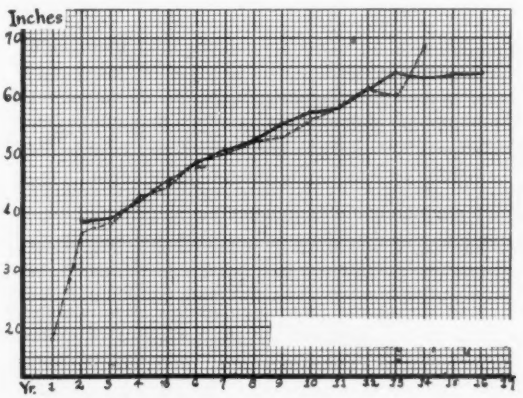


Fig. 9.—The solid line indicates the heights of girls whose reactions for tuberculosis are positive. The broken line indicates the heights of girls whose reactions are negative.

puberty was ascertained for each group and compared with that of a control group from the outpatient department. Graphs were made of the results. The gain in weight of the groups with primary tuberculosis

closely paralleled that of the controls. Figure 6 represents the boys' weight curves and figure 7 the girls' weight curves.

*Gain in Height.*—Similar graphs representing gain in height for both boys and girls and for controls were prepared. The growth in height of the tuberculous children closely paralleled that of the non-tuberculous (figs. 8 and 9).

*Observations Concerning the Chest.*—Frequently repeated auscultation and percussion of the chest of each of these 115 children failed to reveal any abnormality which could not be accounted for by some acute condition, such as an attack of asthma or of acute bronchitis.

## SUMMARY AND CONCLUSIONS

The Vollmer patch test is somewhat less sensitive than the P. P. D. tests. It failed to detect the lesion in 14 of our series, 3 per cent of the entire group or 12 per cent of the positive reactors. It has the advantage of being painless, and it can be administered easily by an office or dispensary assistant. It seems fair to conclude that it is satisfactory for a large scale testing program or in other routine work where the time consumed often deters the physician from administering the P. P. D. or the Mantoux test. In this instance the percentage of error would be only 3. However, if diagnostic accuracy is desired, as in a case of suspected tuberculosis of bone, the P. P. D. tests should be used, because in that instance one would have twelve chances out of one hundred, or one out of eight, of missing the nature of the lesion.

As to the nature of primary tuberculosis of the lungs, I conclude that it is a subclinical disease. It cannot be detected by looking at a child or by making a physical examination or by making a blood count or by keeping a record of the child's weight or growth. History of exposure is the only satisfactory criterion by which it may be suspected. A tuberculin test is the only efficient means of detecting it. Serial roentgenograms are the most satisfactory means of following its course.

The most important question still remains. Will the incidence of destructive tuberculosis and the mortality be higher or lower in the 115 children with positive reactions than in the 345 children with negative reactions to tuberculin? If allergy is the dominant factor in destructive tuberculosis, a higher rate of morbidity and mortality is expected for the 115 positive reactors. On the other hand, if immunity is the dominant factor the morbidity and mortality rates should be lower for the positive reactors.

I expect to make a determined effort to enlarge these groups and to follow as many as possible through adolescence and beyond, in the hope that some additional knowledge may be obtained concerning this highly controversial subject.

# ELECTROCARDIOGRAM IN TOXEMIAS OF PREGNANCY

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AND
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ELECTROCARDIOGRAPHIC patterns suggestive of an acute myocardial infarction of the anterior wall were found in 2 cases in which there was toxemia of pregnancy which resulted in cardiac failure. This unusual and apparently hitherto unreported observation raised the question of the significance of the electrocardiographic abnormalities in toxemia of pregnancy.

A survey of our electrocardiographic files disclosed 12 cases of toxemia of pregnancy without eclampsia. Each case had from one to five records consisting of three limb and two or three chest leads. Examination revealed that they fell into three groups. Group 1 consisted of the 2 cases already mentioned, which presented a classic picture of toxemia of pregnancy and resulted in acute left ventricular failure at the time of labor. Group 2 was made up of 4 cases which did not result in cardiac failure but in which nevertheless changes were manifested in the electrocardiogram. Group 3 consisted of 6 cases in which there was no evidence of cardiac failure and in which no electrocardiographic abnormalities were seen despite the presence of toxemia. Electrocardiograms for 5 normal pregnant women served as controls. None of the patients investigated in this study presented any previous history of cardiac disease.

## ELECTROCARDIOGRAPHIC CHANGES IN TOXEMIA OF PREGNANCY WITH CARDIAC FAILURE

Two cases of electrocardiographic changes in toxemia of pregnancy with cardiac failure were found in our series, and the electrocardiograms are shown in figures 1 and 2.

Aided by the Emil and Fanny Wedeles Fund for Cardiovascular Research.

From the Cardiovascular and Obstetrical Departments of Michael Reese Hospital, Chicago.

The Cardiovascular Department is supported in part by the Michael Reese Research Foundation.

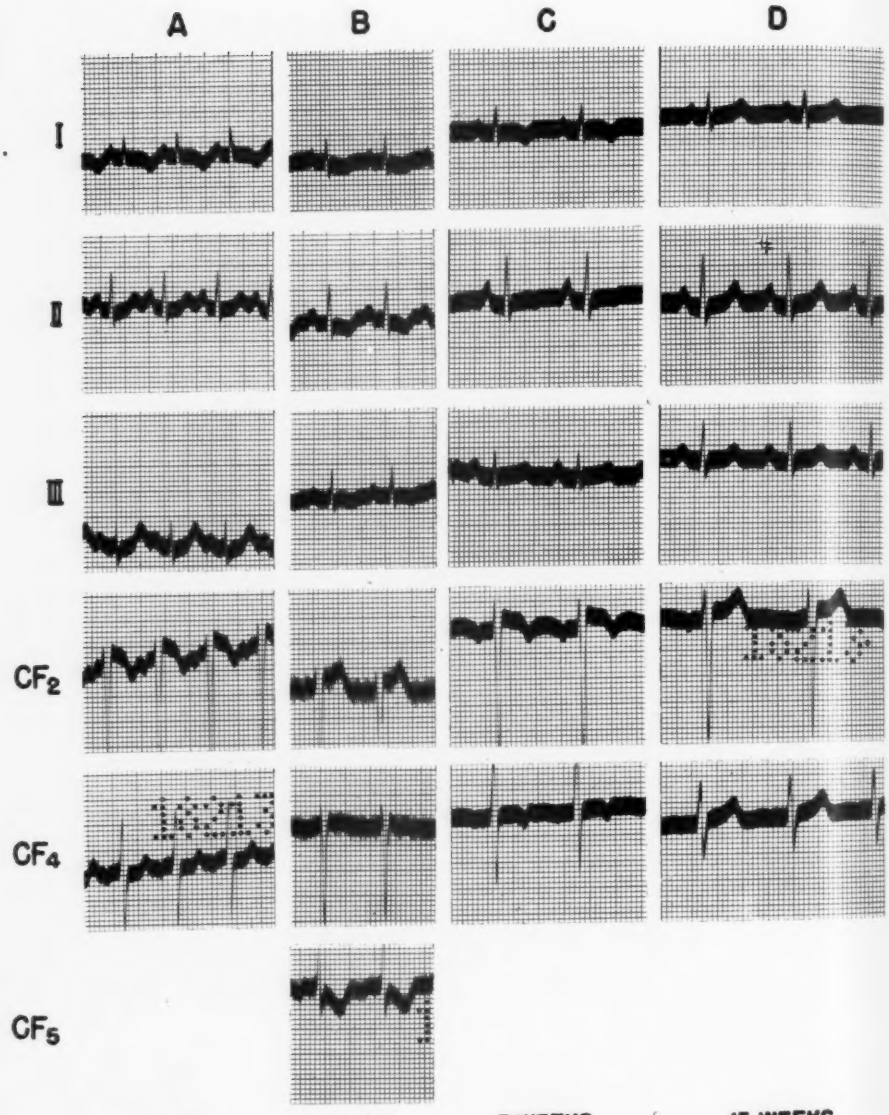


Figure 1

(See legend on opposite page)

The electrocardiograms shown in figure 1 were obtained from a 31 year old white woman, bigravida, primipara, who had had no previous history of cardiac disease and in whom after nine uneventful lunar months of pregnancy a toxemia developed as shown by a hypertension of 170 systolic and 90 diastolic, by the presence of albumin (4 plus) in the urine and by considerable edema in her ankles. At term she went into labor spontaneously, at which time the classic signs and symptoms of acute left ventricular failure manifested themselves. Under a regimen of digitalis, oxygen and morphine sulfate, all signs of cardiac failure disappeared within one week. Four weeks post partum she was discharged from the hospital with a blood pressure of 120 systolic and 70 diastolic, without albuminuria and without edema.

The electrocardiograms shown in figure 2 were obtained from a 35 year old woman, trigravida, bipara, who had had no previous history of cardiac disease and in whom also there developed a classic toxemia of pregnancy. She entered the hospital during the ninth lunar month of pregnancy with a blood pressure of 174 systolic and 104 diastolic, albuminuria (2 plus) and pronounced edema of the lower extremities. During labor, which was induced, the patient experienced acute left ventricular failure. Treatment was similar to that outlined for the preceding patient. Except for a 700 cc. vaginal hemorrhage on the thirteenth postpartum day the patient improved, and she was discharged from the hospital six weeks after entry with a blood pressure ranging from 150 systolic and 85 diastolic to 134 systolic and 80 diastolic, without edema and with an albuminuria of a trace to 1 plus.

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EXPLANATION OF FIGURE 1

Electrocardiograms of a 31 year old white bigravida with toxemia of pregnancy and cardiac failure. *A*, taken one day post partum, shows a sinus tachycardia, low voltage and prolonged electrical systole. In lead I the T wave is inverted, peaked and symmetric; in leads II and III the S-T segments are depressed; in lead III the T wave is upright and peaked; in lead $CF_2$ the T wave is inverted and the R wave is small and in lead $CF_4$ the S-T segment is depressed. *B*, taken two days after *A*, shows a slower rate and electrical systole of normal duration. In lead I the S-T segment is now depressed and the T wave is less inverted; in leads II and III the T waves are now inverted; in lead III the S-T segment is nondeviated; in lead $CF_2$ the T wave is upright; in lead $CF_4$ the S-T segment is nondeviated, the R wave is smaller, the S wave is deeper and the T wave is smaller, and in lead $CF_5$ the S-T segment is depressed and the T wave is inverted. *C*, taken fifteen days after *B*, shows a still slower rate. In leads II and III the P waves are taller, and in lead $CF_2$ the P wave is inverted. In the limb leads the S-T segments are nondeviated. In lead I the T wave is deeper; in lead II the T wave is tiny and diphasic, and in lead III the T wave is upright. The T wave is again inverted in lead $CF_2$ and is now also inverted in lead $CF_4$; the R wave is taller and the S wave is smaller in lead $CF_4$. *D*, taken twelve weeks after *C*, shows a normal contour; the low voltage and the S-T-T abnormalities have disappeared, and the R wave is of normal size in lead $CF_2$. It represents, therefore, complete restitution.

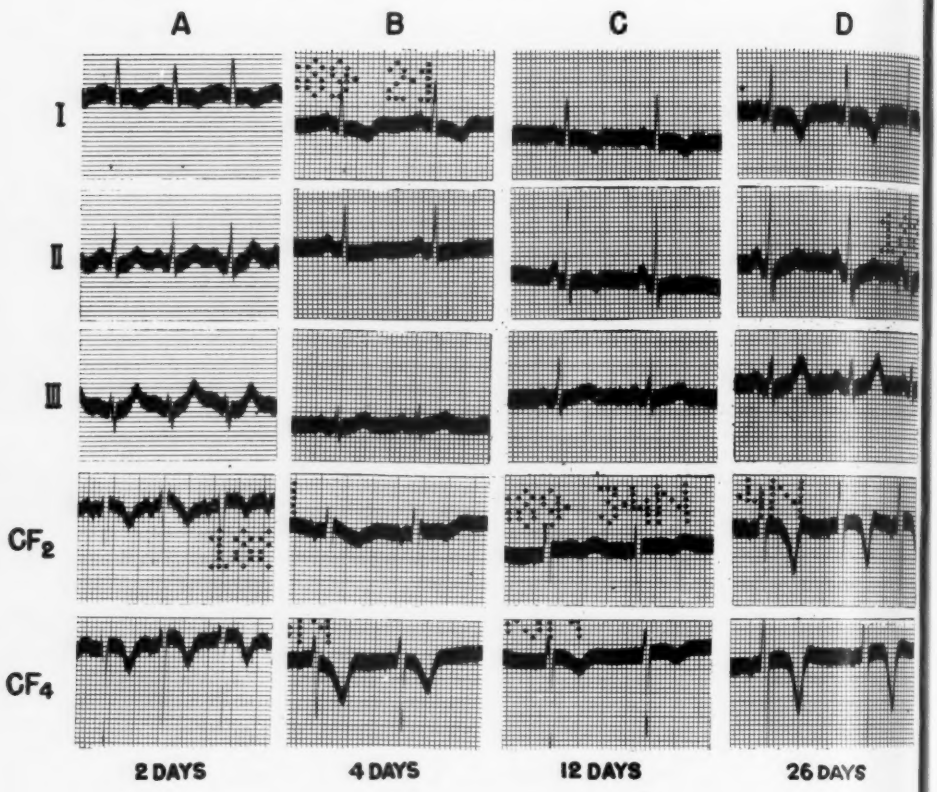


Fig. 2.—Electrocardiograms of a 35 year old white trigravida with toxemia of pregnancy and cardiac failure. *A*, taken two days post partum, shows a sinus tachycardia, and low voltage, an inverted, peaked and symmetric T wave in lead I, a depressed S-T segment in leads II and III and an upright peaked symmetric T wave in lead III. No time lines are present in the limb leads. The R wave is small in leads $CF_2$ and $CF_4$, and the T wave is inverted in these leads. *B*, taken two days after *A*, shows a slower rate, and low voltage is absent. In lead I the S-T segment is now depressed and the T wave is deeper; in lead II the T wave is diphasic, and in lead III the T wave is smaller. The QRS complex is M-shaped in lead $CF_2$; the R wave is taller and the S wave smaller in lead $CF_4$; the S-T segment is nondeviated in leads $CF_2$ and $CF_4$, and the T wave is deeper in lead $CF_4$ and smaller in lead $CF_2$. *C*, taken eight days after *B*, shows the R wave taller in leads II and III, the S-T segment nondeviated in the limb leads, and the T wave inverted in lead II. The R wave is taller in lead $CF_2$, the S wave is deeper in lead $CF_4$, and the T wave is less inverted in leads $CF_2$ and $CF_4$. In leads II and III the P wave is taller. *D*, taken two weeks after *C*, shows the R wave taller in lead I and smaller in lead III. The T wave is now deeply inverted, peaked and symmetric in lead I and upright, peaked and symmetric in lead III. The S-T segment is slightly depressed in the limb leads and the T wave is upright in lead II. The R wave is taller in leads $CF_2$ and $CF_4$, and the T wave is deeply inverted in these leads.

The electrocardiograms obtained from both of these patients are characterized chiefly by the waxing and waning of the symmetrically inverted T wave in leads I, $CF_2$ and $CF_4$, and of an upright symmetric T wave in lead III, the absence of any pronounced S-T deviation and the absence of changes in the QRS complex characteristic of myocardial infarction. One series shows complete restitution to normal within fifteen weeks; the other, unfortunately, could not be followed. These changes simulate those occasionally seen in acute nephritis.[1]

It is interesting that neither patient complained of pain in the chest at any time, although the former noted a sense of compression in her chest which accompanied the pronounced dyspnea at the time of the onset of the acute left ventricular failure. In 13 similar cases of toxemia of pregnancy reported in the literature [2] there was no mention of any complaints of precordial pain. Another interesting observation was that neither patient showed any lowering of the diastolic blood pressure at the time of the cardiac failure. The first patient had a 40 mm. drop of systolic pressure, which returned to its former level within twelve hours. In the second case no drop of the systolic pressure occurred.

These 2 patients, who without any previous history of heart disease experienced a toxemia of pregnancy and cardiac failure at the time of delivery, are not unusual. A review of the literature reveals similar cases.

Thus Gouley, McMillan and Bellet [2a] reported 3 such patients who experienced cardiac failure a short time following delivery. All 3 died, and at autopsy the histopathologic sections of the heart revealed disintegration of the myocardial fibers with lesser involvement of the nuclei. Hemorrhage into these areas was common. A moderate number of lymphocytes and macrophages, occasional neutrophils and eosinophils were present. The pathologic change was not confined to focal destruction. In many fields the structure of the muscles was intact, but the fibers showed definite degenerative changes. The coronary arteries were normal and patent throughout. Death occurred in 3 cases following pulmonary embolism which had its origin in thrombi adherent to the endocardial surface of degenerated cardiac muscle. No other proved source of embolism was found. Gouley and his

1. Langendorf, R., and Pick, A.: Elektrokardiogramm bei akuter Nephritis, Acta med. Scandinav. **94**:1, 1938.

2. (*a*) Gouley, B. A.; McMillan, T. M., and Bellet, S.: Idiopathic Myocardial Degeneration Associated with Pregnancy and Especially the Puerperium, Am. J. M. Sc. **194**:185, 1937. (*b*) Teel, H. M.; Reid, D. E., and Hertig, A. T.: Cardiac Asthma and Acute Pulmonary Edema: Complications of Nonconvulsive Toxemia of Pregnancy, Surg., Gynec. & Obst. **64**:39, 1937. (*c*) Reid, D. E., and Teel, H. M.: Cardiac Asthma and Acute Pulmonary Edema Complicating Toxemias of Pregnancy: Further Observations, J. A. M. A. **113**:1628 (Oct. 28) 1939.

colleagues stated that the electrocardiograms (which were not illustrated) indicated that myocardial damage had occurred in all such patients, but that there was no clue to the cause. Inversion of the T waves was seen in the various limb leads, either singly or in combination, but it did not indicate myocardial infarction. No chest leads were taken in the cases in which autopsies were performed.

Teel, Reid and Hertig [2b] reported a case of a 38 year old octipara who gave no previous history of cardiac disease and in whom an acute toxemia had developed during her seventh month of pregnancy. She experienced an acute pulmonary edema and died shortly afterward. At autopsy the heart, which weighed 335 Gm., showed normal patent coronary arteries. The valves of the heart were normal, and no mural thrombi were found. Microscopic examination revealed pronounced edema of the stroma and occasional moderate-sized areas of the edematous stroma in which there was infiltration of polymorphonuclear and mononuclear leukocytes. Teel and his colleagues did not note any Aschoff bodies, necrosis or fatty degeneration of the myocardium.

Hull and Hafkesbring [3] described a case of a 16 year old Negro primipara who for four weeks prior to delivery presented the picture of extreme anasarca, dyspnea and gallop rhythm. After delivery she began to walk around, and the signs and symptoms of acute pulmonary edema became evident. Therapy was of no avail, and the patient died. At autopsy the heart was found to be enlarged but normal in weight (260 Gm.) The ventricular walls were of normal thickness, and the muscle was pale and friable. There were no valvular lesions. Microscopic examination revealed degeneration of the muscle fibers, interstitial hemorrhage and perivascular accumulation of lymphoid cells. Intense pulmonary edema was present. There was no anatomic evidence of preexisting hypertension. The electrocardiogram (not illustrated) in such cases of "toxic" postpartum cardiac disease was reported to be abnormal but was not characteristic. Low voltage was common and was ascribed to the extensive edema of the heart.

Hull and Hidden [4] illustrated electrocardiograms of the limb leads of patients who had postpartum cardiac failure and showed low or inverted T waves in leads I and II. Following improvement of 1 of these patients the T waves became upright.

In all the preceding cases postmortem examination revealed that the coronary arteries were normal and unobstructed. The pathologic

3. Hull, E., and Hafkesbring, E.: "Toxic" Post Partal Heart Failure, New Orleans M. & S. J. **89**:550, 1937.

4. Hull, E., and Hidden, E.: Post Partal Heart Failure, South. M. J. **31**: 265, 1938.

observations with respect to these hearts were always those of focal myocardial necrosis, edema or infiltration. The few electrocardiograms of limb leads which were obtained for these patients showed occasional inversions of T waves in leads I and II, and a few had low voltage. In the present 2 cases electrocardiograms (consisting of leads I, II, III, $CF_2$ and $CF_4$) showed the evolution of a pattern which might readily be interpreted as that of an atypical acute myocardial infarction of the anterior wall. In view of the pathologic observations in the similar cases reported by others, we believe that these electrocardiographic patterns were produced by focal myocardial necrosis, infiltration or edema rather than by a myocardial infarction secondary to occlusion of a coronary artery. Although occlusion of a coronary artery has been described in young persons, the occurrence in a young woman without any history of antecedent cardiac disease would be most unusual. It would appear that the ultimate prognosis in patients who recover from cardiac failure in toxemia of pregnancy is better than that following coronary disease, and that the electrocardiographic changes are based on focal myocardial necrosis, edema and infiltration rather than on occlusion of a coronary artery and massive myocardial infarction. A correct interpretation of the electrocardiographic pattern in these cases is therefore of practical value.

The changes found in the electrocardiograms obtained for our patients who experienced cardiac failure simulate rather closely those occasionally seen in acute nephritis.[1] This is significant in view of the fact that the pathologic cardiac changes in acute nephritis, while different from those in toxemias of pregnancy (in that they result from vascular damage) may also include edema with occasional inflammatory and degenerative changes of the cardiac muscle and its serous membranes.[5] The electrocardiographic changes found in both conditions are an expression of damage to the myocardium. It is possible that in some cases the damage may not be demonstrable histologically and may yet be sufficient to alter the electrocardiogram. When an electrocardiogram showing this pattern is obtained, the differential diagnosis is to be made by clinical investigation and correlation. Neither of our patients gave any evidence of having nephritis.

An interesting question is that of the cause of the cardiac failure. It is well known that in toxemia of pregnancy the heart is pumping against a tremendous load which consists of (1) an increased resistance in the systemic circuit with its consequent elevated blood pressure, (2) an increased volume of circulating blood and (3) generalized edema which, it must be remembered, is present in the lungs in the form of

5. Baehr, G.: The Nature of Glomerulonephritis, Bull. New York Acad. Med. **14**:53, 1938.

an interstitial edema and which gives rise to a pulmonary hypertension with its consequent strain on the right side of the heart. We believe that the focal myocardial necrosis, edema and infiltration are the essential factors which lead to the myocardial weakening and consequently may act as a precipitating mechanism in the cardiac failure.

Many of the cases reported by others resulted in cardiac failure in a few days to weeks following delivery. One of our patients with toxemia who did not experience cardiac failure is interesting in this respect since her electrocardiogram did not show any abnormalities until two days post partum. We believe that this might be an indication that the evidence of the damage to the myocardium may be present for some time after the emptying of the uterus. The continuation of damage to the myocardium in the early postpartum period might conceivably be responsible for the postpartum failure. This is compatible with the well known fact that toxemia may become more severe at this time. Dexter and Weiss [6] published an electrocardiogram of a hypertensive patient who experienced cardiac failure about one week before labor was induced. The electrocardiogram showed nothing abnormal at that time, but nine days postpartum inversions of T waves in leads I and $IV_F$ were seen. Except for a less inverted T wave in lead I there was no change seen in the electrocardiogram taken nine and one-half weeks post partum. They suggest that these changes may have some bearing on certain cases of obscure postpartum failure.

### ELECTROCARDIOGRAPHIC CHANGES IN TOXEMIA OF PREGNANCY WITHOUT CARDIAC FAILURE

Only 4 out of 10 cases of toxemia of pregnancy in which cardiac failure did not develop showed electrocardiographic abnormalities, and none of these were as pronounced as those in our 2 cases in which cardiac failure developed. In none of these cases were patterns present resembling an atypical acute infarction of the anterior wall or acute nephritis. Three of these 4 cases are illustrated in figures 3, 4 and 5.

The electrocardiograms shown in figure 3 were obtained from a 25 year old primigravida who during the last month of her pregnancy experienced a severe toxemia as indicated by a blood pressure of 220 systolic and 140 diastolic, generalized edema, blurring of vision and albuminuria. For two days following low cervical cesarean section the blood pressure maintained itself at 178 systolic and 130 diastolic to 155 systolic and 105 diastolic. Within a week the blood pressure returned to its level before pregnancy of 118 systolic and 88 diastolic. Except for

6. Dexter, L., and Weiss, S.: Preeclamptic and Eclamptic Toxemia of Pregnancy, Boston, Little, Brown & Company, 1941, p. 218.

a mild cystitis, the postpartum course was uneventful, and the patient was discharged sixteen days following delivery without edema; her urine gave a reaction of 1 plus for albumin, and her blood pressure

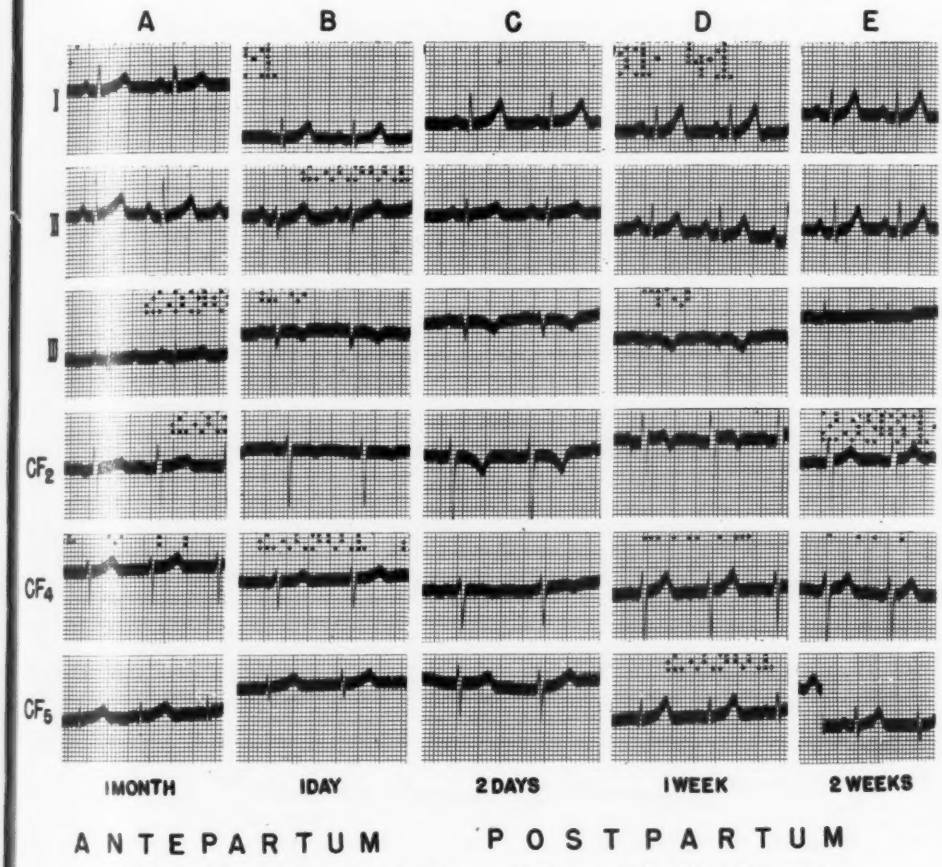


Fig. 3.—Electrocardiograms of a 25 year old Negro primigravida with toxemia of pregnancy but without cardiac failure. *A*, taken a month ante partum, shows a normal record with left axis shift. *B*, taken one day ante partum, shows low voltage. The R wave is smaller in leads I and II. A small S wave appears in lead I and a deep S wave in leads II and III; the T wave has become inverted in leads III and $CF_2$, and the R wave is smaller in lead $CF_2$. *C*, taken two days post partum, shows the R wave taller in leads I and II, the S wave absent in lead I and smaller in lead II, the T wave taller and peaked in lead I, deeper in leads III and $CF_2$ and small and inverted in $CF_4$, and the S wave deeper in $CF_5$. *D*, taken five days after *C*, shows the T wave taller in leads I and II, the R wave taller in lead II, the S wave absent in lead II, the T wave deeper in lead III, the R wave taller in lead $CF_2$, the S wave absent in lead $CF_5$ and the T wave diphasic in lead $CF_2$, upright in lead $CF_4$ and taller in lead $CF_5$. *E*, taken one week after *D*, differs only in minor details from *A* and therefore represents complete restitution.

was normal. This is an example of a woman who experienced a severe toxemia of pregnancy without subsequently having cardiac failure; however, electrocardiographic changes occurred two days following delivery.

The electrocardiograms shown in figure 4 were obtained from a 34 year old Negro septigravida, sextipara, who showed very mild symptoms of toxemia and who had pronounced fluctuations in blood pressure. A single reading recorded in the fourth month was 150 systolic and 80

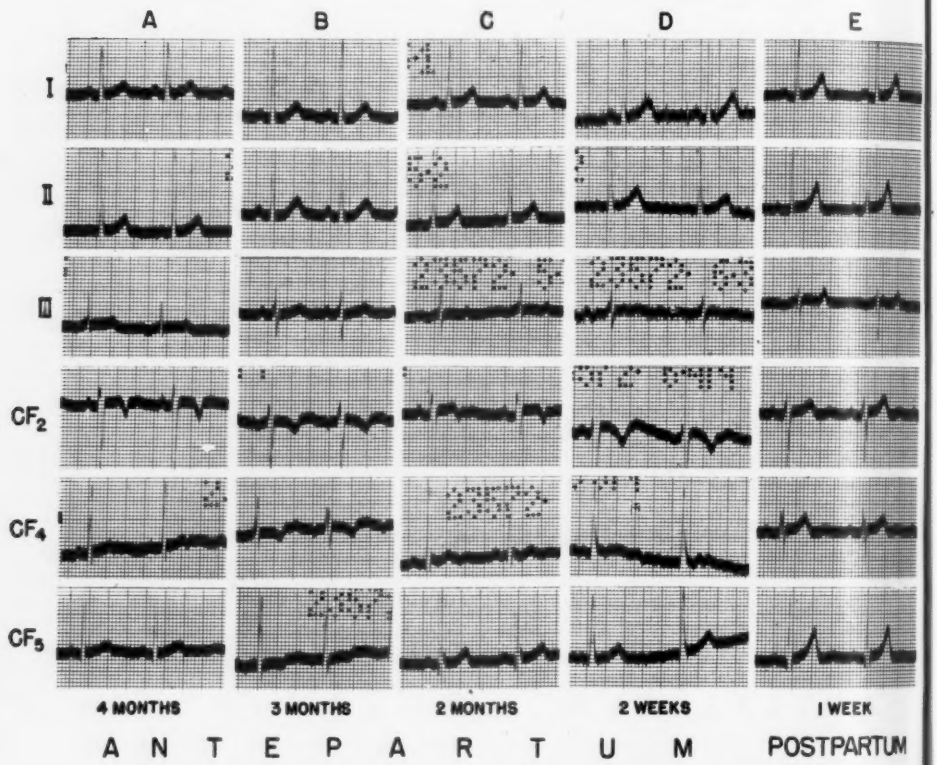


Fig. 4.—Electrocardiograms of a 34 year old Negro septigravida with mild toxemia of pregnancy but without cardiac failure. *A*, taken four months ante partum, shows as its only abnormalities an inverted T wave in lead $CF_2$ and a diphasic or notched T wave in lead $CF_4$. *B*, taken one month later, shows an S wave in lead III, a T wave that is broader and inverted in lead $CF_2$, inverted in lead $CF_4$ and diphasic in lead $CF_5$, an S wave that is smaller in lead $CF_2$ and more noticeable in lead $CF_4$ and an R wave that is smaller in lead $CF_4$. *C*, taken one month later, has reverted practically to the configuration in *A*. *D*, taken two weeks ante partum, shows a deeper T wave in lead $CF_2$ and a smaller R wave in this lead. (There is an extracardiac oscillatory artefact in this record.) *E*, taken one week post partum, shows a normal record with left axis shift, the abnormalities of the T wave in previous records being absent.

diastolic; during a two week period of observation at the hospital in the sixth month the blood pressure ranged from 190 systolic and 110 diastolic to 120 systolic and 80 diastolic; similar fluctuations were observed during the last two weeks before delivery, with readings ranging from 210 systolic and 110 diastolic to 120 systolic and 70 diastolic. After delivery the blood pressure was from 150 to 180 systolic and from 70 to 90 diastolic. We hesitated to ascribe the electrocardiographic changes found in this case to the mild toxemia of pregnancy. However, their disappearance after delivery together with the drop in blood pressure seem to justify the inclusion of this case as one of toxemia of pregnancy.

The electrocardiograms shown in figure 5 illustrate an instance of a very mild toxemia of pregnancy in a patient who did not experience cardiac failure. These records were obtained from a 16 year-old Negro primigravida in whom during the last trimester of her pregnancy there began to develop a mild toxemia. She entered the hospital at term with a blood pressure of 145 systolic and 94 diastolic; her urine gave a reaction of from 1 to 3 plus for albumin, and there was a slight edema of the ankles. During the first three days following an uneventful spontaneous delivery her blood pressure ranged from 150 systolic and 110 diastolic to 142 systolic and 85 diastolic. By the tenth postpartum day no albuminuria or edema was present, and the blood pressure had returned to its level before pregnancy of 116 systolic and 80 diastolic.

The fourth patient with abnormalities in the electrocardiogram had a moderately severe toxemia and showed a transitory first degree auriculoventricular block (P-R interval of 0.22 second) in a record taken six days following delivery. Other records taken nine and five days ante partum, as well as three weeks post partum, showed the P-R interval ranging between 0.14 and 0.20 second. Except for the transitory first degree auriculoventricular block, there were no electrocardiographic abnormalities.

Abnormalities in the electrocardiogram do not occur in all cases of toxemia of pregnancy. Our electrocardiographic files contain six lead records of 6 patients with varying degrees of toxemia in none of whom were electrocardiographic abnormalities found. None of these women experienced cardiac failure.

### THE ELECTROCARDIOGRAM IN NORMAL PREGNANCY

It is not possible to state that all cases of toxemia of pregnancy in which cardiac insufficiency develops do show electrocardiographic abnormalities. Our own 2 cases did, and those reported in the literature apparently also did. Furthermore, it is not possible to state that all abnormalities seen in cases of toxemia of pregnancy are due to the

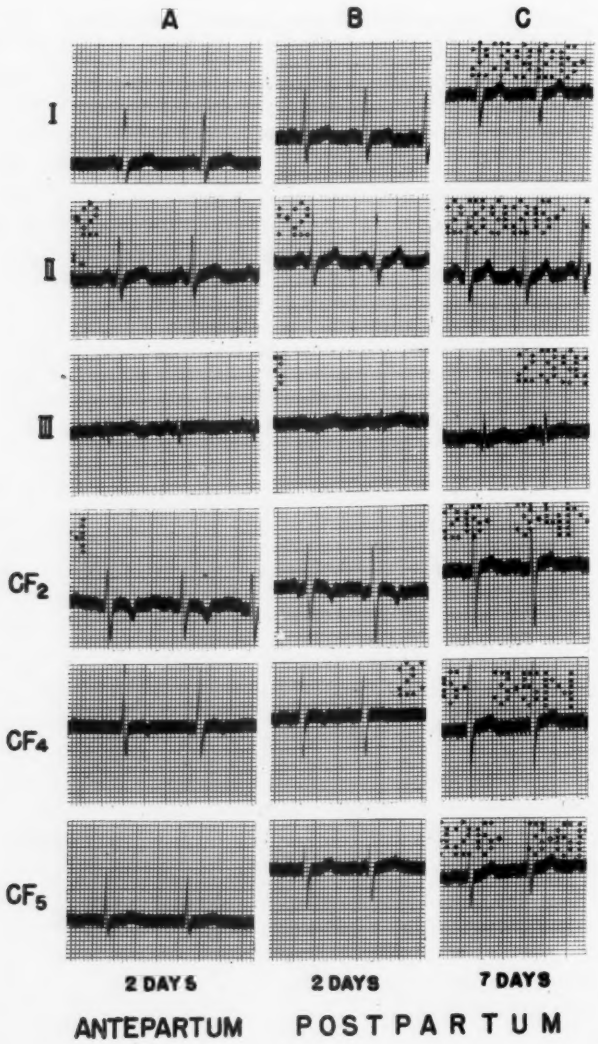


Fig. 5.—Electrocardiograms of a 16 year old Negro primigravida with mild toxemia of pregnancy but without cardiac failure. *A*, taken two days ante partum, shows normal limb leads, but the T wave is inverted in leads $CF_2$ and $CF_4$. *B*, taken two days post partum, shows a faster rate and a deeper S wave in leads I, II and $CF_5$, but otherwise *B* is similar to *A*. *C*, taken five days after *B*, shows the S wave deeper in leads I and II, the QRS complex in lead III upright and small, and the T wave upright in all leads. The inversions of the T wave in previous records are those associated with pregnancy.

toxemia. It is known that left axis shift, a prominent Q and a deep inversion of T waves in lead III develop in normal pregnancy.[7]

In our own series electrocardiograms were available for 5 normal women during the last month of their pregnancy. Except for the expected axis shift due to the altered position of the heart, no abnormalities were found. One record, however, is of possible significance in connection with the inversions of the T wave found in the cases of toxemia. This electrocardiogram is shown in figure 6 and was obtained for a 17 year old Negro girl who had a perfectly normal pregnancy and delivery. It shows a transitory inversion of the T wave in lead $CF_2$. This finding suggests that such inversions of the T wave in the chest leads may be normal occurrences in pregnancy.

Thus, in 1 of our 7 patients with toxemia and also in 1 of our 5 normal pregnant women inversion of the T wave occurred in leads $CF_2$ and $CF_4$. The inversions of the T wave in these leads were seen in the last month of pregnancy and persisted two days post partum. The T wave reverted to its normal upright form one week post partum. Since the uterus empties and the diaphragm descends when delivery takes place, the change in the T wave after the second postpartum day eliminated the position of the heart as the sole factor in the causation of the inversions of the T wave. Dilatation of the heart secondary to the plethora which occurs in the last trimester of pregnancy and resolves slowly in the postpartum period may be the important factor. The role of the hormonal imbalance associated with pregnancy is not understood. It is interesting that the patient from whom the electrocardiogram illustrated in figure 5 was obtained, a 16 year old patient with a mild toxemia, had a blood pressure of 145 systolic and 94 diastolic when the inversion of the T wave was present in leads $CF_2$ and $CF_4$. One week later, when the blood pressure returned to a normal of 116 systolic and 80 diastolic, these T waves became upright. In the record taken one week post partum the S wave in lead I and the R wave in lead III had become larger, which indicates that an axis shift to the right had occurred.

The frequency of this inversion of the T wave in leads $CF_2$ and $CF_4$ in our small series is of the same order as that found by Thomson, Cohen and Hamilton,[7a] who used a chest lead which corresponds most closely

7. (*a*) Thomson, K. J.; Cohen, M. E., and Hamilton, B. E.: Studies on the Circulation in Pregnancy: V. Lead Five of the Electrocardiogram in Pregnancy, Including Normal, Cardiac and Toxemic Women, Am. J. M. Sc. **196**:819, 1938. (*b*) Carr, F. B.; Hamilton, B. E., and Palmer, R. S.: The Significance of Large Q in Lead III of the Electrocardiogram During Pregnancy, Am. Heart J. **8**:519, 1933.

with lead $CF_3$ (the chest electrode was placed in the fourth interspace 5 cm. to the left of the midsternal line). They found that 7.7 per cent of normal pregnant women had an inverted T wave in this lead which reverted to an upright T wave some time following delivery. The postpartum electrocardiogram from a normal patient which they illustrated

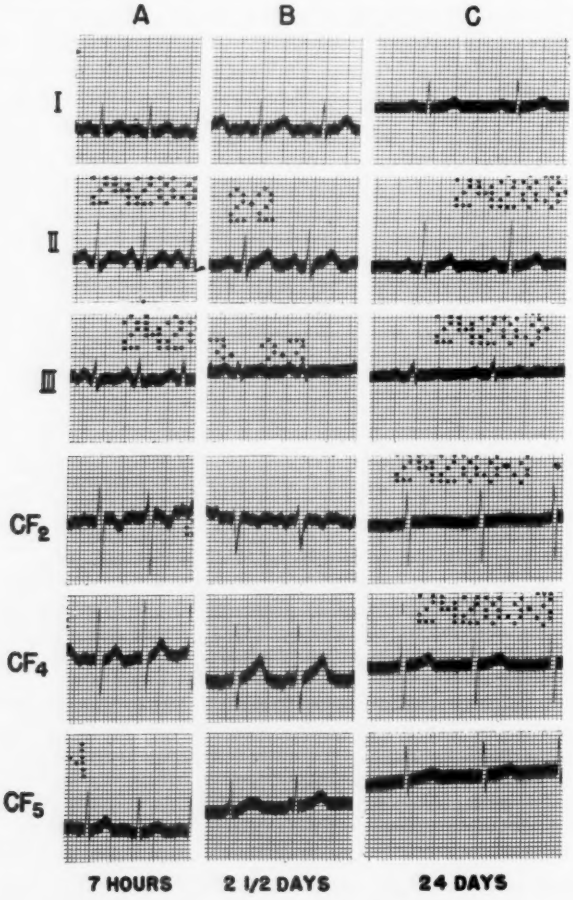


Fig. 6.—Electrocardiograms of a 17 year old Negro primigravida with a normal pregnancy. *A*, taken seven hours ante partum, shows a sinus tachycardia and an inversion of the T wave in lead $CF_2$. *B*, taken two and one-half days post partum, shows a slower rate and a T wave taller in leads I and II, less inverted in lead $CF_2$ and taller in lead $CF_4$; also a smaller R in $CF_2$, *C*, taken three weeks after *B*, shows a normal record with sinus rhythm and left axis shift; the changes in the T wave therefore are associated with pregnancy.

was taken six weeks after delivery. No statement was made as to how soon after delivery this reversion occurs.

## SUMMARY

This study has indicated that abnormalities in the electrocardiogram in the toxemias of pregnancy are of two sorts, namely: (1) changes which occur with equal frequency in normal pregnancy and are therefore not related to the toxemia of pregnancy and (2) changes which do not occur in normal pregnancy and are therefore related to the toxemia.

At times the electrocardiographic changes are pronounced in toxemias of pregnancy, especially when heart failure develops. In such cases the pattern may closely resemble that seen in acute nephritis and may simulate an atypical pattern of acute infarction of the anterior wall.

The possible causes of these electrocardiographic abnormalities are discussed, and the practical significance of their evaluation is presented.

## CONCLUSIONS

1. Patients with toxemia of pregnancy who experience cardiac failure show electrocardiographic abnormalities. Some of those who do not experience cardiac failure also show changes.

2. Focal myocardial necrosis, edema and infiltration secondary to toxemia of pregnancy may give an electrocardiographic picture which simulates that of acute nephritis or of an atypical acute myocardial infarction of the anterior wall. The myocardial involvement, as shown by changes in the T wave, may continue after delivery and is a possible factor in postpartum cardiac failure.

3. Inversion of the T wave in leads $CF_2$ and $CF_4$ occurring during the last trimester of pregnancy and reverting to its normal upright form within one week following delivery is possibly a result of dilatation of the heart. This occurs in a small percentage of normal and toxemic patients.

4. Transient first degree auriculoventricular block may occur (1 case is described which occurred in the postpartum period of a patient with toxemia of pregnancy).

5. A better ultimate prognosis may be made for a patient who recovers from cardiac failure secondary to toxemia of pregnancy as contrasted with the prognosis for a patient who recovers from a coronary occlusion with myocardial infarction. A correct interpretation of the electrocardiogram is important.

# PROTHROMBIN LEVEL OF PERIPHERAL BLOOD AND STERNAL MARROW

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DESPITE the tremendous strides made in recent years in the understanding of the properties of prothrombin, its metabolic cycle remains a matter of conjecture. As far as is known, the liver is the site of production of prothrombin, and the precursor of thrombin is liberated into the circulating blood continuously and in excess. Of the fate and possible additional functions of prothrombin practically nothing is known. The manner in which vitamin K and dicoumarin (3,3′-methylene-bis-[4-hydroxycoumarin]) exert their respective influences on the prothrombin–elaborating system likewise remains obscure.

The evidence to prove that the liver is the major, if not the sole, locus for the synthesis of prothrombin is as yet neither complete nor conclusive. The conception is based on the demonstration that hepatocellular damage, artificially induced or occurring clinically, is accompanied with prothrombinopenia. Which of the components of the liver, the hepatic parenchymatous cells or the elements of the reticuloendothelial system encompassed by this most versatile organ, performs the function remains an unanswered question.

In a quest for evidence in substantiation or negation of these premises we undertook to determine whether a relationship could be established in respect to the production of prothrombin between reticuloendothelial activity and function presumably of the liver. This was accomplished by an indirect approach, namely, by a comparison of the prothrombin clotting time of plasmas obtained simultaneously from the peripheral venous blood and from the sternal bone marrow.

Forty-seven subjects were studied. They were all patients suffering with chronic disorders, their diagnoses varying from the common cardiovascular diseases and arthritides to the rarities of coarctation of the aorta and ochronosis. All adult age groups were represented, and the two sexes were equally divided.

From the Third (New York University) Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine.

An aspiration of sternal marrow and a venipuncture were made in each case, within a few minutes of each other. On 1 (subject 10) two such operations were done, one before and the other while he was under the influence of dicoumarin, the total comparisons therefore numbering 48. During each venipuncture, 4.5 cc. of blood was drawn into a syringe containing 0.5 cc. of tenth-molar sodium oxalate solution and the two were thoroughly admixed. After the needle was in the sternal marrow space 4.5 cc. of material was similarly aspirated into a syringe containing 0.5 cc. of the sodium oxalate solution. The aspirated material was found to be a composite of sternal marrow, a small amount of fatty substances and blood. This was well evidenced by differential cell counts and the thin supernatant layer of lipid material. These specimens were promptly centrifuged, clear plasma pipetted off and the estimation of prothrombin time made. All estimations were made in duplicate.

The method used for estimation of the prothrombin time was described in a previous publication of this series.[1] It included estimation of the prothrombin time of both whole and diluted (12.5 per cent) plasma. A thromboplastic agent of standardized activity prepared from desiccated fresh rabbit lung was used.

Comparative measurement of the prothrombin time was made on 28 patients receiving no medication. The data obtained in these cases are presented in table 1. There are no significant differences in the figures for whole plasma, and only 2 show differences in excess of five seconds in the prothrombin time of diluted (12.5 per cent) plasma.

The method of selecting a means to determine what constitutes a significant difference is worthy of discussion. The prothrombin times of the diluted plasma are much greater than those of the unmodified plasma and are subject to frequent and pronounced variations in patients with a disease, though in normal persons these values remain remarkably constant. Thus, the meaningful figures in these studies are the differences between the prothrombin time of plasma and of marrow of each subject rather than the variation between a given figure and the average of the group. It would lend additional support if the values were considered not only from the standpoint of the absolute figure but also in relation to the total time. Thus, we consider the minimum significant differences in the presence of normal dilute plasma prothrombin time (forty seconds) to be four seconds, which in relation to the total time is 10 per cent, while in the presence of prothrombinopenia the minimum significant difference becomes greater, depending on the extent of prolongation of the prothrombin time, and at least 10 per cent of the absolute value of the latter. For example, a difference of less than twenty seconds in a prothrombin time of two hundred seconds for dilute plasma would be considered not significant. The same principle is to be applied to differences in prothrombin time of unmodified plasma, except that the values are restricted to a range too narrow to reveal fine differences.

The average difference just described corresponds most closely to the statistical mean deviation, and we have adopted twice the relationship of the average difference to the average total time as the percentage of minimum significant difference.

## RESULTS

Table 1 reveals the following salient features: The averages for plasma and marrow approximate each other remarkably in both the

1. Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: Procedure and Clinical Interpretations, Proc. Soc. Exper. Biol. & Med. **50**:85, 1942.

whole and the diluted plasma. The averages of the differences in both phases are very small, and the differences are about equally divided between plasma greater and less than marrow, leading us to conclude that solely chance factors predominated in determining the quantity and direction of these small variations.

TABLE 1.—*Data for Twenty-Eight Subjects Who Received No Medications Known to Alter Prothrombin Levels*

| | Whole * | | | | Dilute * | | | |
|---|---|---|---|---|---|---|---|---|
| Subject No. | Plasma, Sec. | Marrow, Sec. | Difference, Sec. | Plasma>Marrow—Plasma<Marrow+ | Plasma, Sec. | Marrow, Sec. | Difference, Sec. | Plasma>Marrow—Plasma<Marrow+ |
| 1 | 13.6 | 12.6 | −1.0 | = | 41.0 | 47.0 | +6.0 | < |
| 2 | 13.3 | 14.7 | +1.4 | = | 34.5 | 36.2 | +1.7 | = |
| 3 | 13.8 | 13.6 | −0.2 | = | 44.4 | 41.4 | −3.0 | = |
| 4 | 14.4 | 14.6 | +0.2 | = | 44.2 | 46.4 | +2.2 | = |
| 5 | 12.2 | 11.6 | −0.6 | = | 33.2 | 31.2 | −2.0 | = |
| 6 | 15.2 | 15.5 | +0.3 | = | 45.2 | 50.6 | +5.4 | = |
| 7 | 13.4 | 13.4 | 0.0 | = | 31.6 | 33.8 | +2.2 | = |
| 8 | 17.2 | 16.8 | −0.4 | = | 62.2 | 63.0 | +0.8 | = |
| 9 | 12.4 | 11.4 | −1.0 | = | 43.0 | 38.2 | −4.8 | = |
| 10 | 15.4 | 13.0 | −2.4 | > | 51.4 | 49.4 | −2.0 | = |
| 11 | 13.4 | 15.0 | +1.6 | < | 44.6 | 45.1 | +0.5 | = |
| 12 | 12.6 | 12.9 | +0.3 | = | 40.0 | 38.4 | −1.6 | = |
| 13 | 15.0 | 16.7 | +1.7 | < | 46.0 | 44.0 | −2.0 | = |
| 14 | 14.9 | 13.9 | −1.0 | = | 34.6 | 37.7 | +3.1 | = |
| 15 | 12.2 | 12.9 | +0.7 | = | 28.8 | 32.1 | +3.3 | = |
| 16 | 13.2 | 14.1 | +0.9 | = | 35.1 | 37.7 | +2.6 | = |
| 17 | 12.1 | 12.1 | 0.0 | = | 34.0 | 40.0 | +6.0 | < |
| 18 | 13.8 | 14.0 | +0.2 | = | 48.1 | 43.8 | −4.3 | = |
| 19 | 12.7 | 12.1 | −0.6 | = | 39.5 | 34.3 | −5.2 | > |
| 20 | 13.6 | 11.8 | −1.8 | > | 40.0 | 43.1 | +3.1 | = |
| 21 | 14.6 | 13.8 | −0.8 | = | 51.8 | 53.4 | +1.6 | = |
| 22 | 14.8 | 15.4 | +0.6 | = | 36.7 | 37.4 | +0.7 | = |
| 23 | 13.8 | 13.2 | −0.6 | = | 37.1 | 35.9 | −1.2 | = |
| 24 | 14.6 | 13.9 | −0.7 | = | 36.7 | 41.3 | −4.6 | = |
| 25 | 14.9 | 15.2 | +0.3 | = | 36.5 | 37.4 | −0.1 | = |
| 26 | 16.6 | 17.1 | +0.5 | = | 73.2 | 69.3 | −3.9 | = |
| 27 | 13.3 | 13.6 | +0.3 | = | 59.8 | 55.6 | −4.2 | = |
| 28 | 16.4 | 15.2 | −1.2 | = | 59.5 | 55.1 | −4.4 | = |
| Average | 14.0 | 13.9 | 0.76 | | 43.2 | 43.5 | 2.95 | |
| | M>P, 14 subjects, average 0.64 sec. | | | | M>P, 15 subjects, average 2.88 sec. | | | |
| | M<P, 14 subjects, average 0.88 sec. | | | | M<P, 13 subjects, average 3.0 sec. | | | |

* Note that the averages for plasma and marrow approximate each other remarkably in both the whole and the diluted plasma.

Table 2 is a frequency distribution of the data of table 1 and shows a fair parallelism of concentration and distribution of figures for plasma and marrow in both phases. The curves formed by charting the figures in each column are akin to curves of normal distribution, skewed somewhat to the right, as might be expected since there is more opportunity for a random scatter above the usual figures than below. The mean, medium and mode as well as mean deviation, standard deviation and probable error were all computed and charted. All these characteristics for both plasma and marrow lie in close proximity. The

mean, medium and mode have the usual relationship to each other found in most curves of normal distribution.

The foregoing facts tend to confirm rather definitely our impression that the character and amount of any deviations and discrepancies in these measurements are more than adequately attributable to fortuitous circumstances, such as the inevitable small differences in any experimental method using physical measurement.

Having thus demonstrated that there is no significant difference in the prothrombin level of peripheral blood and of bone marrow, we might logically progress one step further and conclude that the reticulo-

TABLE 2.—*Frequency Distribution* *

| Group in Seconds | Number of Readings in Group: Whole Plasma | Whole Marrow | Group in Seconds | Number of Readings in Group: Dilute Plasma | Dilute Marrow |
|---|---|---|---|---|---|
| 11.0-11.9 | 0 | 3 | 28-30.9 | 1 | 0 |
| 12.0-12.9 | 6 | 5 | 31-33.9 | 2 | 3 |
| 13.0-13.9 | 10 | 8 | 34-36.9 | 6 | 3 |
| 14.0-14.9 | 6 | 4 | 37-39.9 | 3 | 6 |
| 15.0-15.9 | 3 | 5 | 40-42.9 | 3 | 3 |
| 16.0-16.9 | 2 | 2 | 43-45.9 | 5 | 4 |
| 17.0-17.9 | 1 | 1 | 46-48.9 | 2 | 2 |
| | | | 49-51.9 | 2 | 2 |
| | | | 52-54.9 | 0 | 1 |
| | | | 55-57.9 | 0 | 2 |
| | | | 58-60.9 | 2 | 0 |
| | | | 61-63.9 | 1 | 1 |
| | | | 64-66.9 | 0 | 0 |
| | | | 67-69.9 | 0 | 1 |
| | | | 70-72.9 | 0 | 0 |
| | | | 73-75.9 | 1 | 0 |
| | Mean, 14.0 | Mean, 13.9 | | Mean, 43.2 | Mean, 43.5 |
| | Median, 13.8 | Median, 13.8 | | Median, 40.5 | Median, 41.3 |
| | Mode, 13+ | Mode, 13+ | | No mode | Mode, 37+ |
| | M.D., 1.07 sec. | M.D., 1.22 sec. | | M.D., 1.84 sec. | M.D., 7.45 sec. |
| | S.D., 1.35 sec. | S.D., 1.52 sec. | | S.D., 10.2 sec. | S.D., 9.8 sec. |
| | P.E., 0.9 sec. | P.E., 1.0 sec. | | P.E., 6.8 sec. | P.E., 6.6 sec. |

M.D. = mean deviation (from median); S.D. = standard deviation; P.E. = probable error.

* Note the fair parallelism of concentration and distribution of plasma and marrow figures in both phases.

endothelial system is not involved in the production of prothrombin. There are several arguments which might be used against such a conclusion. One might claim that this comparative method is not trustworthy, although it has been used satisfactorily before. The venous blood departing from an organ may be found to have a higher concentration of some constituent than arterial blood entering the same organ if that constituent is manufactured or stored in the organ, e. g., angiotonin and the kidney. Measurement of prothrombin concentrations of pulmonary arterial and pulmonary venous blood in animals has shown a lower concentration in the venous blood, leading certain workers to believe that the lung is one organ which serves to destroy

prothrombin.[2] An argument for specificity of action of the reticuloendothelial cells in varying locales is untenable in the light of present knowledge. One might wonder whether the process of elaboration of prothrombin is slow and/or irregular, thus making it impossible by the means at hand to measure differences in concentration from that of the peripheral blood. Then, again, it is possible that a higher concentration of prothrombin in the marrow may be obscured by dilution of the aspirated marrow with whole blood from the venous channels and with lipid material.

In order to circumvent the last two possibilities, it was decided to study another group of patients receiving high doses of synthetic vitamin K. This dosage serves the purpose of considerably increasing the prothrombin level of the blood at least for a few days and therefore presumably augments the production of prothrombin. Table 3 is a compilation of the results determined in this group of 8 patients.

TABLE 3.—*Changes in the Plasma and Marrow Times After Vitamin-K-Like Quinones* *

| Subject No. | Prothrombin Time, Whole, Seconds | | Plasma> Marrow— Plasma< Marrow+ | > than Significant < than Significant | Prothrombin Time, Diluted 12.5%, Seconds | | Plasma> Marrow— Plasma< Marrow+ | > than Significant < than Significant |
|---|---|---|---|---|---|---|---|---|
| | Plasma | Marrow | | | Plasma | Marrow | | |
| K1 | 12.0 | 12.5 | +0.5 | = | 36.5 | 38.0 | +1.5 | = |
| K2 | 12.4 | 10.9 | —1.5 | > | 37.6 | 36.2 | —1.4 | = |
| K3 | 11.5 | 11.9 | +0.4 | = | 35.0 | 39.9 | +4.9 | = |
| K4 | 11.8 | 11.1 | —0.7 | = | 33.4 | 35.0 | +1.6 | = |
| K5 | 13.7 | 13.1 | —0.6 | = | 33.4 | 33.5 | +0.1 | = |
| K6 | 10.6 | 11.2 | +0.6 | = | 40.0 | 35.4 | —4.6 | = |
| K7 | 9.6 | 10.4 | +0.8 | = | 36.8 | 42.5 | —5.7 | < |
| K8 | 11.0 | 10.7 | —0.3 | = | 37.9 | 41.0 | +3.1 | = |
| Average | 11.6 | 11.5 | Diff. 0.68 | | 36.3 | 37.8 | Diff. 2.9 | |

* The quinone definitely lessened the averages of the plasma and marrow prothrombin times as contrasted with the control studies (table 1).

All these subjects had had large doses of vitamin-K-like quinone (25 to 100 mg. a day orally for a week or 72 to 200 mg. intravenously twenty-four hours prior to the sternal marrow puncture). This table shows that the quinone was efficacious, for the averages of the prothrombin times of plasma and marrow in both phases are decidedly less than in the control group (table 1). The average differences and percentage average differences remain about the same as in the control group (table 4), as do the general characteristics of the group.

2. Andrus, W. DeW.; Lord, J. W., Jr., and Kaeur, J. T.: Studies on the Fate of Plasma Prothrombin, Science **91**:48, 1940.

This is evidence that even during a period of rapidly increasing production of prothrombin no difference of any import is found between marrow and peripheral blood. This observation adds strong support to the contention that the bone marrow and reticuloendothelial system are not involved in the metabolism of prothrombin.

TABLE 4.—*Comparison of Average Prothrombin Time*

| | No Medication | Vitamin K | Dicoumarin |
|---|---|---|---|
| Average plasma, whole | 14.0 seconds | 11.6 seconds | 18.8 seconds |
| Average marrow, whole | 13.9 seconds | 11.5 seconds | 20.8 seconds |
| Average plasma, diluted | 43.2 seconds | 36.3 seconds | 84.7 seconds |
| Average marrow, diluted | 43.5 seconds | 37.8 seconds | 99.4 seconds |
| Average difference, whole | 0.76 seconds | 0.68 seconds | 2.0 seconds |
| Average difference, diluted | 2.95 seconds | 2.9 seconds | 14.6 seconds |
| Per cent average difference, whole | 5.4 per cent | 5.9 per cent | 10 per cent |
| Per cent average difference, diluted | 6.9 per cent | 7.8 per cent | 15.9 per cent |

A third series of measurements was made on 7 patients who had effective doses of dicoumarin (400 to 600 mg.) given in the forty-eight hour period preceding sternal puncture. As seen in table 5 the tendency in this group was not only the expected prolongation of prothrombin time but a dissociation of effect on plasma and marrow, with 71 per cent (5 of 7) having a significant difference in the undiluted fraction and 86 per cent (6 of 7) in the diluted fraction. In table 4

TABLE 5.—*Changes in the Prothrombin Time After Ingestion of 400 to 600 Mg. of Dicoumarin* *

| Subject Number | Prothrombin Time, Whole, Seconds | | Plasma > Marrow — Plasma < Marrow + | > than Significant < than Significant | Prothrombin Time, Diluted (12.5%), Seconds | | Plasma > Marrow — Plasma < Marrow + | > than Significant < than Significant |
|---|---|---|---|---|---|---|---|---|
| | Plasma | Marrow | | | Plasma | Marrow | | |
| D1 | 17.2 | 19.3 | +2.1 | < | 59.1 | 69.9 | +10.8 | < |
| D2 | 14.2 | 16.0 | +1.8 | < | 44.6 | 51.3 | + 6.7 | < |
| D3 | 40.4 | No clot | ? | < | 231.0 | 274.0 | +43.0 | < |
| D4 | 36.6 | 41.4 | +4.8 | < | 95.5 | 118,4 | +22.9 | < |
| D5 | 16.2 | 16.9 | +0.7 | = | 53.4 | 60.8 | + 7.4 | < |
| D6 | 13.8 | 16.3 | +2.5 | < | 48.7 | 51.3 | + 2.6 | = |
| D7 | 14.8 | 14.7 | −0.1 | = | 60.5 | 69.5 | + 9.0 | < |
| Average | 18.8 | 20.8 | | | 84.7 | 99.4 | | |
| Average difference | | | 2.0 | | | | 14.6 | |

* Note the dissociation of effect on plasma and marrow prothrombin times.

the important facts concerning each of the 3 groups thus far discussed are presented, and the only percentage average difference to exceed the previously established significant level is in the dicoumarin column.

It is difficult to conceive that this difference is due to inhibition of prothrombin formation in the marrow, for that would be almost totally inconsistent with the results of the first two group studies. It would be much more consonant with our general observation to postulate

that the dicoumarin serves to hasten the process of destruction of prothrombin, and it would appear that this is most probably done by the reticuloendothelial system.

The fourth and last group of subjects were studied in a like manner to determine the effect of simultaneous doses of synthetic vitamin K and dicoumarin. Table 6 presents results for this group. All the

TABLE 6.—*Effect of Simultaneous Doses of Quinone and Dicoumarin on the Prothrombin Studies*

| Subject Number | Prothrombin Time, Whole, Seconds | | Plasma > Marrow — Plasma < Marrow + | > than Significant < than Significant | Prothrombin Time, Diluted (12.5%) Seconds | | Plasma > Marrow — Plasma < Marrow + | > than Significant < than Significant |
|---|---|---|---|---|---|---|---|---|
| | Plasma | Marrow | | | Plasma | Marrow | | |
| KD1 | 13.3 | 12.2 | −1.1 | = | 44.0 | 49.0 | + 5.0 | = |
| KD2 | 12.5 | 13.9 | +1.4 | < | 53.0 | 61.3 | + 8.3 | < |
| DK3 | 19.0 | 20.8 | +1.8 | < | 69.3 | 80.3 | +11.0 | < |
| DK4 | 27.9 | 29.7 | +1.8 | = | 164.5 | 191.6 | +27.1 | < |
| DK5 | 26.2 | 29.4 | +3.2 | < | 86.2 | 101.7 | 15.5 | < |

subjects received massive doses of the quinone (150 to 250 mg.) intravenously and amounts of dicoumarin varying from 100 to 600 mg. in the order of their listing on the chart. This series yielded results similar to those of the group receiving dicoumarin alone (refer to table 7), 60 per cent (3 of 5) significant prolongations of the prothrombin time for marrow in the undiluted plasma fraction and 80 per cent (4 of 5) in the diluted plasma. The only patient with no pro-

TABLE 7.—*Comparative Changes in the Plasma and Marrow Prothrombin Times*

| | Whole | | | Diluted | | |
|---|---|---|---|---|---|---|
| | Plasma > Marrow | P = M | P < M | Plasma > Marrow | P = M | P < M |
| Patients with no medication. | 2 (7%) | 24 (86%) | 2 (7%) | 1 (4%) | 25 (89%) | 2 (7%) |
| Patients with vitamin K..... | 1 (14%) | 7 (86%) | 0 (0%) | 0 (0%) | 7 (86%) | 1 (14%) |
| Patients with dicoumarin.... | 0 (0%) | 2 (29%) | 5 (71%) | 0 (0%) | 1 (14%) | 6 (86%) |
| Patients with vitamin K and dicoumarin..... | 0 (0%) | 2 (40%) | 3 (60%) | 0 (0%) | 1 (20%) | 4 (80%) |

longation in either phase was KD 1, who had received only 100 mg. of dicoumarin, the smallest amount administered to any of the group. Though the end effects of synthetic vitamin K and dicoumarin are oppposite, one increasing prothrombin concentration, and the other decreasing it, the manner of action of the latter does not seem to be directly antagonistic to the former. Even when the dose of dicoumarin is small and that of the quinone massive, the reaction of the dicoumarin usually predominates in that the prothrombin time of marrow plasma decreases disproportionately to that of the peripheral blood, although

the large amount of synthetic vitamin K may have prevented the absolute prothrombin time from rising prominently. The impression is gained that the dicoumarin produces the effect not solely by prohibiting the formation of prothrombin but also by facilitating its destruction. If the former were true we would expect to find not a differential prothrombin concentration in marrow and plasma but rather a symmetric decrease in both, for in circumstances of normal synthesis of prothrombin it is symmetric in both. On the other hand, if the action of dicoumarin were also to help destroy prothrombin in the reticuloendothelial system, the concentration at the marrow would decrease faster in the marrow than in the blood regardless of whether or not synthetic vitamin K were given.

## CONCLUSIONS

1. From the evidence presented we are led to conclude that prothrombin is not elaborated by the reticuloendothelial system and therefore is probably not a function of the hepatic parenchyma.

2. Prothrombin is equally distributed in the sternal marrow and in the more actively circulating peripheral blood stream and may be much more widely disseminated throughout the body than is generally realized.

3. Vitamin K accelerates the production of prothrombin and the excess which results is also equally distributed in the marrow and peripheral blood.

4. Dicoumarin causes a more pronounced decrease in prothrombin of the marrow than in prothrombin of the peripheral blood. The evidence compiled herein is suggestive that this is due to the destruction of prothrombin, most likely by the reticuloendothelial system.

5. When dicoumarin is given simultaneously with synthetic vitamin K, even if the former is in relatively small amounts and the latter in massive quantities, the action of the dicoumarin usually predominates.

The thromboplastin used in this study was supplied by Dr. Ralph Overman, of the Maltine Company. Miss Shirley Schwalb gave technical assistance.

# Progress in Internal Medicine

## SYPHILIS

### A Review of the Recent Literature

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*(Concluded from page 364)*

PENICILLIN

*Experimental.*—An organized cooperative study of the effect of penicillin in experimental syphilis of rabbits is under way in several laboratories in this country (Eagle, Mahoney, Chesney, Carpenter, Rake, Fleming). Here are being explored the essential time-dose relationships, the combination of penicillin with other chemotherapeutic agents, the effect of different penicillin fractions and of possible impurities and commercial penicillin and optimum treatment schedules. Except as cited later, however, none of the mentioned investigators has as yet published results, which may be expected to be forthcoming during this next year. Meanwhile, only two very unsatisfactory papers dealing with the general problem of penicillin in early syphilis of rabbits have appeared, those of Selbie and Simon,[62] working in Great Britain, and Ercoli and Lafferty,[63] in this country.

Selbie and Simon [62] have employed penicillin in the treatment of 9 rabbits with testicular chancres. One animal received a single intramuscular injection of 400 units per kilogram of weight. Five animals received three injections at three hourly intervals with a total dose ranging from 1,500 to 30,000 units per kilogram (total duration of treatment six hours). Another animal received five daily injections to a total of 2,500 units per kilogram. The remaining 2 were given three injections at three hourly intervals on each of four successive days to a total of 12,000 units per kilogram. Spirochetes disappeared from the lesions within one to seven days in 8 of the 9 animals, and lesions healed completely in 3, though there was only temporary regression

62. Selbie, F. R., and Simon, R. D.: The Effect of Penicillin on Treponema Pallidum Infection in Rabbits, Brit. J. Exper. Path. **25**:229 (Dec.) 1944.

63. Ercoli, N., and Lafferty, L. C.: The Anti-Spirochetal Activity of Penicillin in Experimental Infections, Proc. Soc. Exper. Biol. & Med. **57**:4 (Oct.) 1944.

or no effect in the other 6. In 5 of the treated animals whose lesions showed only temporary regression, spirochetes could again be found by dark field examination in thirty-five to forty-nine days after treatment. No information is provided as to eventual cure, since transfers of lymph nodes were not performed. It is certain, however, that 6 of the 9 animals were not cured, since lesions either failed to heal at all or subsequently relapsed. The authors studied blood levels in 5 rabbits after the intramuscular injection of graded doses and believe that it requires approximately five times as much penicillin in the rabbit as in man to produce comparable bacteriostatic titers. They are inclined to attribute the unfavorable results obtained in their animals to this factor. Actually, however, their poor results seem to us to be based on too short a duration of treatment and on too irregular spacing of multiple injections, so that maintained blood levels were not produced.

Ercoli and Lafferty[63] found in 9 animals that the intravenous injection of the sodium salt of penicillin in single doses of 33,000 to 47,000 units per kilogram resulted in the disappearance of T. pallidum, as determined by dark field examination, in experimental rabbit syphilis within an eighteen hour period. A similar effect could be obtained with an approximate total dose of 16,000 units per kilogram administered intravenously in four divided doses at unstated but probably irregular intervals, over a seventy-two hour period. However, even total doses of 132,000 to 282,000 units per kilogram of weight given in four to six injections over forty-eight to seventy-two hours were not curative, since in 4 of 9 animals transfers of lymph nodes produced syphilis at an unstated interval after treatment. Nothing is said of the other 5 animals.

In view of the demonstrated efficacy of penicillin in the treatment of syphilis and other spirochetal diseases, it is important to determine whether this therapeutic effect requires the intervention of body cells, or whether it is due to a direct spirocheticidal action. With other micro-organisms, inhibitory, bacteriostatic and an actual bactericidal action have been described.

Eagle and Musselman[64] have tested the spirocheticidal activity of penicillin against four cultured strains of T. pallidum. They summarize by saying:

1. Penicillin was found to be actively spirocheticidal *in vitro* against the Reiter, Kazan, Nichols, and Noguchi strains of so-called *S. pallida*, and a strain of mouth spirochetes. The threshold concentration was 0.01 unit per cc. (1-160,000,000 penicillin). The rate and degree of action increased with the concentration of penicillin up to a level of approximately 0.1 to 0.25 unit per cc., which rendered more than

64. Eagle, H., and Musselman, A. D.: The Spirocheticidal Action of Penicillin in Vitro and Its Temperature Coefficient, J. Exper. Med. **80**:493 (Dec.) 1944.

99 per cent of the organisms nonviable within 12 hours. Higher concentrations did not appreciably accelerate the effect.

2. Within the range $4 \times 10^4 - 10^7$ organisms per cc., the initial rate at which the spirochetes were killed was not affected by their number. Consistent with that observation, no demonstrable penicillin was found or inactivated by thick suspensions. The amount of penicillin required to sterilize suspensions of varying density nevertheless varied to a large extent with the initial number of organisms. This was only in part due to the progressive deterioration of the penicillin with prolonged incubation; and the persistence of organisms resistant to the drug, and perhaps an adaptative change after prolonged exposure to penicillin, may be contributing factors.

3. The organisms remained actively motile for a period of 8 to 24 hours after they had been rendered non-viable by the action of penicillin. Even 500 units of penicillin per cc., or approximately 10,000 times an effectively spirocheticidal concentration, did not accelerate that delayed immobilization. It follows that, although penicillin rapidly renders the organisms non-viable, the metabolic system affected is not immediately essential to the life of the cell, and the motility and presumably other vital functions remain unaffected for a significant number of hours.

4. The rate at which the organisms were killed by penicillin increased with temperature in the range 8—40° C. With an original inoculum of $10^6$ spirochetes per cc., the percentage of organisms surviving after 24 hours at 39—40°, 36—37°, 32—33°, 22—23°, and 8° C. was 0.02, 0.2, 1, 10, and 100 respectively; and those results were independent of the concentration of penicillin in the range 0.25 to 250 units per cc. If these observations with a non-pathogenic organism *in vitro* are applicable to the pathogenic organism *in vivo*, they suggest that the combined use of fever and penicillin in the treatment of syphilis may be more effective than either alone.

There is no published information concerning the exact composition of the various brands of crude penicillin. It is already known, however, that there is more than one type of crystalline penicillin. At least three of those fractions, F, G and X, have been mentioned in the current literature [65] without details of the chemistry of production. It has been stated that the proportions of these fractions present in commercial penicillin vary depending on the method of production. In view of these facts the question arises as to which penicillin fraction is responsible for the therapeutic effects, or indeed whether some substance other than penicillin itself might not be responsible. Dunham and Rake [66] performed experiments in vitro and in vivo to determine whether penicillin G or impurities present in partially purified penicillin may contribute to the antisyphilitic action of the mixtures. The immobilizing activities in vitro of ampules of commercial penicillin, old preparations of low potency and an aluminum oxide adsorbate of low potency obtained

65. Dale, H.: Address of the President of the Royal Society, Science **101**:23 (Jan. 12) 1945.

66. Dunham, W. B., and Rake, G.: The Relative Activity of Partially Purified Penicillin and of Crystalline Penicillin G on Treponema Pallidum, Am. J. Syph., Gonor. & Ven. Dis. **29**:214 (March) 1945.

in the chromatographic purification of commercial penicillin and crystalline penicillin G were compared. Crystalline penicillin G employed in a concentration of 8,800 units per cubic centimeter for two hours in vitro had little or no effect on the motility of T. pallidum. Under the same conditions, a solution containing 2,200 units per cubic centimeter of the least pure penicillin preparation immobilized all of the spirochetes. A substance in partially purified penicillin that immobilized spirochetes could be concentrated by adsorption on aluminum oxide and recovered by elution. The concentration of the substance in partially purified penicillin that was active against spirochetes in vitro was only very slightly, if at all, reduced by incubation at 37 C. (98.6 F.) in the presence of a weak solution of penicillinase over a period of eleven days. Under these conditions a large proportion of the penicillin present is inactivated. The immobilization of spirochetes in vitro by partially purified penicillin was due, therefore, to one or more of the impurities present. Penicillin acid, a product of the hydrolysis of pure penicillin G, was inactive.

Virulent spirochetes exposed to 1,100 units per cubic centimeter of partially purified penicillin were noninfectious for rabbits despite persistent motility (compare the observation of Eagle and Musselman that penicillin renders culture spirochetes nonviable while motility is still present) while spirochetes similarly exposed to 800 units per cubic centimeter of crystalline penicillin G produced orchitis in rabbits.

Partially purified penicillin, 330 units per milligram, protected a large proportion of rabbits from local and generalized infection when 66,000 units per kilogram of body weight were administered intramuscularly five hours after a suspension of spirochetes had been rubbed into an incision in the skin of the back. The same dose of crystalline penicillin G failed to protect. That crystalline penicillin G does have some antisyphilitic action was shown by the prevention of local syphilitic lesions in a large proportion of rabbits treated with injections of 166,000 units per kilogram of weight. In the same experiment, however, an aluminum oxide adsorbate of partially purified penicillin showed greater activity.

The general trend of the experiments in vitro and in vivo which have been discussed indicates that crude penicillin is more effective in the treatment of syphilis in rabbits than is highly purified penicillin when an equal number of units is employed. This suggests that certain impurities or fractions of penicillin, other than penicillin G, contribute to the antisyphilitic action of commercial penicillin.

These experiments also suggest that, because of the large quantities that would be required, it would not be practicable at the present time to employ penicillin in a single dose systemically as a prophylactic against syphilis in human beings.

This is disturbing information to those interested in the use of penicillin for syphilis. In acute infections (e. g., gonorrhea, pneumonia, meningitis) commercial penicillin as now available seems eminently satisfactory, and it is perhaps of academic interest only as to which component of the mixture of many is actively bactericidal. In the more chronic infections, e. g., subacute bacterial endocarditis and syphilis, it may prove to be of paramount importance to determine whether it is penicillin itself, and if so which fraction thereof, or some impurity contained in commercial penicillin which is actually most effective. Work is in progress on these points, but data are not as yet available.

Heilman[67] studied the therapeutic effect of streptomycin on experimental relapsing fever in mice and leptospirosis icterohaemorrhagica in hamsters. The investigator used large doses of streptomycin in both sets of experiment. He concluded that streptomycin exerted a considerable protective effect against experimental infections with both Borrelia novyi and Leptospira icterohaemorrhagiae. However, the drug was relatively less effective than penicillin in the treatment of these infections. This is the first report which would indicate that streptomycin has antispirochetal properties.

*Methods of Administration.* — Absorption-Delaying Methods: Although clinical effectiveness of penicillin has been well established, a completely satisfactory method of administration of the drug has not been found.

The intramuscular injection of aqueous or saline solutions, most commonly employed, results in high blood levels of penicillin for brief periods and necessitates frequent injections. The intermittent intravenous method also results in transitory high levels and necessitates repeated venipunctures. The continuous intravenous or intramuscular drip, although maintaining a satisfactory level, is technically difficult, immobilizes the patient and is frequently productive of local reactions.

Romansky and Rittman[68] feel that a method of administration of penicillin which would decrease the rate of absorption and prolong the duration of an effective level in the blood, in addition to being of minimum inconvenience to the patient, would be of importance, especially in the treatment of syphilis. To this end they experimented with suspensions of penicillin in refined peanut, sesame, cottonseed, corn, castor and olive oils, and protamine zinc in an attempt to produce its prolonged action in rabbits after intramuscular injection. All of these resulted

67. Heilman, F. R.: Streptomycin in the Treatment of Experimental Relapsing Fever and Leptospirosis Icterohaemorrhagica (Weil's Disease), Proc. Staff Meet., Mayo Clin. **20**:169 (May 30) 1945.

68. Romansky, M. J., and Rittman, G. E.: Penicillin: I. Prolonged Action in Beeswax-Peanut Oil Mixture; II. Single Injection of Treatment of Gonorrhea, Bull. U. S. Army M. Dept., October 1944, no. 81, p. 43.

in more prolonged blood levels than were obtained with salt solutions of the drug.

Having in mind the pioneer work of Code and his associates [69] on the absorption-delaying effect of beeswax dissolved in various oils in the administration of histamine and other substances, Romansky turned to this expedient:

After preliminary trials with varying amounts of yellow wax U. S. P. (beeswax) in different oils, the most satisfactory results were obtained with a beeswax–peanut oil mixture. Because calcium penicillin is less hygroscopic than the sodium salt and forms better mixtures with the oils, it was used for the majority of experiments. The method of suspending penicillin in beeswax–peanut oil mixture is given.

As a pilot experiment rabbits weighing from 2.5 to 3.5 Kg. were given injections intramuscularly of 5,000 to 10,000 Oxford units of penicillin contained in 1 cc. of beeswax–peanut oil mixture, and blood assays were made to determine the duration and maintenance of effective levels. This experiment showed that after the administration of 5,000 units of sodium penicillin in saline solution the blood level rapidly reaches 1.25 units per cubic centimeter and rapidly drops to zero within two hours. When the same amount of penicillin is suspended in peanut oil alone, a level of 0.312 unit per cubic centimeter of blood is reached within approximately one-half hour and is maintained for a longer period than with the saline solution, approximately three hours. If, on the other hand, the penicillin is suspended in beeswax–peanut oil mixture, penicillin can be demonstrated for as long as six hours.

Human subjects were then given single injections of 41,500 to 66,400 Oxford units of penicillin intramuscularly in the buttocks. These doses were contained in 2 to 2.4 cc. of beeswax–peanut oil mixtures. Again, satisfactory blood levels were maintained for six to seven hours.

Since the experimental results with the penicillin beeswax–peanut oil mixture were so favorable, it was deemed advisable to treat 12 patients with gonococcic urethritis. Three of these had had no previous treatment, and 9 were resistant to sulfonamide drugs. All were treated with a single injection of the penicillin beeswax–peanut oil mixture. Doses varied between 51,250 and 100,000 Oxford units contained in 2 to 3 cc. of the mixture. As the total dosage of penicillin was increased, the period over which penicillin could be demonstrated in the blood was also prolonged. When 100,000 units was given in a single injection, penicillin could be demonstrated in the blood for as long as ten hours and was excreted in the urine for as long as twenty-five hours. There was only 1 failure in the 12 patients treated. This was in a previously

69. Code, C. F.; Gregory, R. E. L., and Kottke, F. J.: Prolonged Action of Desoxycorticosterone Acetate, Am. J. Physiol. **133**:240 (Jan.) 1941.

untreated patient who received the smallest dose of penicillin, 51,250 Oxford units. The size of the dose does not entirely explain the failure, since the levels obtained in the blood compare favorably with the levels of patients who received somewhat larger doses of penicillin and were cured.

None of the patients complained of local pain or irritation in the region of injection.

Intramuscular injections of 500 to 1,000 Oxford units of penicillin, contained in 0.05 to 0.10 cc. of 3 per cent beeswax–peanut oil mixture, were given to 10 hamsters twice a day for five days. The animals were then killed at the rate of 1 a week for the purpose of examining the tissue from the site of injection. There was no necrosis of muscle demonstrated, and only minimal changes were noted. Generally small oil cysts from 1 to 2 mm. in diameter could be identified after the seventh day. By the thirtieth day the walls of the cysts were less cellular, and some were partially collapsed.

A later paper by Romansky, Murphy and Rittman [70] expands the results of the single injection treatment of gonorrhea with calcium penicillin in peanut oil–beeswax and is mentioned here because of the possible applicability of the method to syphilis.[71] Among 100 patients receiving a single dose of 100,000 units, 93 were cured; the 7 who were not cured responded to a second single injection of 150,000 units. All of 75 patients receiving a single dose of 150,000 units were cured.

Blood levels and duration and amount of excretion of penicillin in the urine after larger single injections of penicillin are graphically recorded in the figure. Romansky [72] has permitted us to reproduce this figure, which will appear in an article to be published in the *New England Journal of Medicine.*

Fears that beeswax might contain pollens and therefore create a hazard in the treatment of pollen-sensitive sufferers from hay fever or asthma have been allayed by careful experimentation by Gay.[73]

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70. Romansky, M. J.; Murphy, R. J., and Rittman, G. E.: Single Injection Treatment of Gonorrhea with Penicillin in Beeswax-Peanut Oil: Results in One Hundred and Seventy-Five Cases, J. A. M. A. **128**:404 (June 9) 1945.

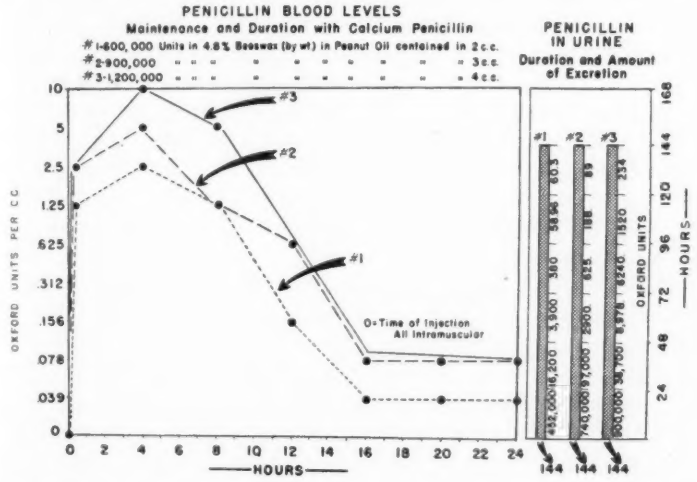
71. Calcium penicillin so prepared in peanut oil—beeswax (4.8 per cent beeswax by weight) is now commercially available. One firm calls this product "Delicillin" ("del", delayed). Physicians should be cautioned that while it has been experimentally employed in the treatment of a small number of patients with early syphilis, the results are not yet available, and the method cannot as yet be recommended for general use.

72. Romansky, M. J.: New England J. Med., to be published.

73. Gay, L. N.: The Nonantigenic Property of Beeswax, J. Allergy **16**: 192 (July) 1945.

Various other methods of delaying absorption or retarding excretion of penicillin (bibliography given by Bronfenbrenner and Favour [74]) have been tried, but none seems as promising, in syphilis at least, as Romansky's method.

Oral or Rectal Administration: A number of papers have already appeared dealing with the oral or rectal administration of penicillin (Libby [75]; Burke, Ross, and Strauss [76]; György and his associates [77]; Loewe and his group [78]; McDermott and associates,[79] and Charney and others [80]—see comments following). All of these indicate that when




Penicillin in blood and duration and amount of excretion in urine after large single injections of the drug.

74. Bronfenbrenner, J., and Favour, C. B.: Increasing and Prolonging Blood Penicillin Concentrations Following Intramuscular Administration, Science **100**: 673 (June 29) 1945.

75. Libby, R. L.: Oral Administration of Penicillin in Oil, Science **101**:178 (Feb. 16) 1945.

76. Burke, F. G.; Ross, S., and Strauss, C.: Oral Administration of Penicillin: A Preliminary Report, J. A. M. A. **128**:83 (May 12) 1945.

77. György, P.; Vandegrift, H. N.; Elias, W.; Colio, L. G.; Barry, F. M., and Pilcher, J. D.: Administration of Penicillin by Mouth: Preliminary Report, J. A. M. A. **127**:639 (March 17) 1945.

78. Loewe, L.; Alture-Werber, E., and Rosenblatt, P.: Administration of Penicillin by Rectal Suppository: Preliminary Note, J. A. M. A. **128**:18 (May 5) 1945.

79. McDermott, W.; Bunn, P. A.; Benoit, M.; DuBois, R., and Haynes, W.: Oral Penicillin, Science **101**:228 (March 2) 1945.

80. Charney, J.; Alburn, H. E., and Bernhart, F. W.: Urinary Excretion of Penicillin in Man After Oral Administration with Gastric Antacids, Science **101**:251 (March 9) 1945.

penicillin is administered orally at appropriately spaced intervals, either as such in solution or in capsules or in combination with various antacids or suspended in oils with or without beeswax, blood levels may be obtained comparable to those achieved after a parenterally administered dose about one fifth as large. Absorption from the rectum is, however, poor. The details of these papers are purposely omitted here, since my colleagues and I believe that, except in most exceptional circumstances, the oral treatment of syphilis with penicillin or any other drug is at present indefensible. Syphilitic patients, regardless of intelligence, cannot be trusted to take oral medication at the appropriate intervals (with penicillin, every two to three hours day and night) for the necessary length of time. The prescription is sometimes not filled at all; if the drug is obtained, the urgent necessity for regularity in taking it is often—perhaps nearly always—quickly forgotten, and the bottle reposes peacefully on the bathroom shelf. This is to say nothing of the fact that if used orally in syphilis, prohibitively larger and expensive amounts of penicillin would certainly be required—perhaps a minimum of 10,000,000 units and a possible maximum of several hundred million units.

The Intrathecal Administration of Penicillin: That penicillin cannot be demonstrated in the cerebrospinal fluid after parenteral administration has frequently been demonstrated. This has led to the routine intrathecal administration of the drug in most cases of bacterial meningitis and in situations in which there appears to be some advantage to the method. In neurosyphilis the desirability of intrathecal treatment with other substances than penicillin has long been a controversial subject, on which there is still no complete unanimity of opinion. Nevertheless it was inevitable that penicillin should be so emphasized in neurosyphilis; unfortunately so, since careful studies have not been carried out as to safe doses, either for animals or for men.

Pilcher and Meacham [81] have studied the effects of intracisternal injection of penicillin in normal dogs, using doses of 50 to 500 units. Such injections produced transitory "meningeal reactions," whose intensity was roughly proportional to the dose. These reactions apparently consisted in an increase in the spinal fluid cell count ranging roughly from 1,000 to 16,000 cells per cubic millimeter, occurring at its maximum two to six hours after injection. No significant neurologic or other clincal phenomena were obseved. In a footnote Pilcher and Meacham say that later observations to be published elsewhere have shown that much larger and more frequent intrathecal doses are well tolerated. So far as we

81. Pilcher, C., and Meacham, W. F.: The Chemotherapy of Intracranial Infections: III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin, J. A. M. A. **123**:330 (Oct. 9) 1943.

are aware, these later observations have not yet appeared in print. It is known that other experimental studies, also so far unpublished, have shown that penicillin locally applied to the central nervous system (brain or spinal cord) has certain irritating properties which may produce acute or chronic reactions with convulsions, coma and death.

A safe dosage of penicillin intrathecally for man has not yet been determined. Most workers suggest a maximum of 20,000 units. That there may be grave risk in the administration of this or of larger amounts is exemplified by certain papers dealing with the treatment of neurosyphilis, discussed in later paragraphs. There is also a strong suggestion in studies of neurosyphilis so far reported (see later comments on Nelson and Duncan) that the intrathecal use of penicillin in neurosyphilis is unnecessary.

For the time being and until further and more detailed clinical and experimental studies have been completed, we feel strongly that the average physician would be wise to avoid the method entirely in neurosyphilis.

*The Penetration of Penicillin into Various Tissues, Especially the Eye.*—Several groups of workers have studied the penetration of penicillin into various structures of the eye after the parenteral and local administration of penicillin. Struble and Bellows [82] found that penicillin could be detected in the eyeball of dogs within fifteen minutes after 12,800 units per kilogram was injected intravenously. The ocular tissues and fluids are listed in accordance with the concentrations in them of penicillin, in decreasing order: extraocular muscles, sclera, conjunctiva, tears, chorioretinal layer, aqueous humor, vitreous humor and cornea. The crystalline lens contained none. Levels in the aqueous humor and the less vascularized tissues, such as the conjunctiva and sclera, after their initial sharp rise within the first fifteen minutes, continued to increase slowly until the end of the first hour. Barely a trace of penicillin remained in the eyeball after three hours.

When penicillin was administered intravenously and intramuscularly in amounts comparable to therapeutic doses (1,500 units per kilogram), there was such a slight concentration in the fluids and tissues of the eye that it was not measurable by the usual methods.

After subconjunctival injection (500 to 5,000 units in 0.25 cc. of saline solution) high and even enormous concentrations were reached in the cornea, iris, ciliary body, conjunctiva and sclera. There was a moderate amount in the aqueous and vitreous humors. No drug was demonstrated in the posterior half of the chorioretinal layer and the

82. Struble, G. C., and Bellows, J. G.: Studies on the Distribution of Penicillin in the Eye, and Its Clinical Application, J. A. M. A. **125**:685 (July 8) 1944.

lens. After a constant corneal bath of penicillin (20,000 units per cc.), the results were similar, except that the concentrations in the aqueous, cornea, vitreous and iris with the ciliary body were higher, and those in the conjunctiva and sclera were lower.

Von Sallmann and Meyer [83] compared the penetration of penicillin into the aqueous humor of rabbits after local application by means of iontophoresis with that following a corneal bath with and without wetting agents. The ionization method increased the concentration of penicillin in the aqueous ten times as much as the corneal bath and about eight times as much as the corneal bath with the addition of a wetting agent, Aerosol 1B (dibutyl sodium sulfosuccinate). After a single iontophoretic application of a 0.25 per cent solution of the sodium salt of penicillin, the aqueous exhibited an antibacterial activity for almost four hours; after a single corneal bath with a solution of the same concentration, the antibacterial activity continued little more than two hours.

Leopold and LaMotte [84] found that, although penicillin locally applied to the eye in solution or in ointment fails to penetrate into the aqueous humor of the normal rabbit eye after one instillation, it does penetrate readily into the anterior chamber of rabbit eyes with corneal abrasions or ulcers. The concentrations obtained in the anterior chamber of the eyes with inflamed or abraded corneas after local instillation of 500 units of penicillin per cubic centimeter in isotonic solution of sodium chloride or 500 units per gram of ointment base exceed the probable antibacterial level of 0.15 unit per cubic centimeter. They believe that it is not necessary to resort to iontophoresis, the corneal bath technic or subconjunctival injection in order to obtain effective concentrations of penicillin in the aqueous humor of eyes with infected corneal ulcers or abrasions. Instillation of a solution of penicillin (500 units per cubic centimeter of isotonic solution of sodium chloride) or penicillin ointment (500 units per gram) need be made only once every two hours to the conjunctival cul-de-sac to maintain high concentrations in the aqueous humor. It was also demonstrated that repeated applications of penicillin solution do not significantly retard regeneration of corneal epithelium.

These three studies are of potential (but not as yet demonstrated) importance in the local penicillin treatment of interstitial keratitis, a manifestation of syphilis which does not respond readily to the parenteral administration of the drug.

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83. von Sallmann, L., and Meyer, K.: Penetration of Penicillin into the Eye, Arch. Ophth. **31**:1 (Jan.) 1944.

84. Leopold, I. H., and LaMotte, W. O., Jr.: Penetration of Penicillin in Rabbit Eyes with Normal, Inflamed and Abraded Corneas, Arch. Ophth. **33**:43 (Jan.) 1945.

More important to the syphilotherapeutist, however, are the only experiments so far recorded concerning the concentrations of penicillin in various tissues of the body. Struble and Bellows [82] treated an unstated number of dogs with a single large (12,800 units per kilogram) intravenous injection (corresponding to a single dose of nearly 1,000,000 units to an adult) and killed the animals one, two and three hours afterward. The body tissues and fluids examined are listed in accordance with the concentration in them of penicillin, in decreasing order: kidney, small intestine, lung, buccal mucosa, bile, skin, liver, adrenal gland, heart, voluntary muscle and spleen. None, or only traces, could be found in nerve tissue, cerebral dura and bone marrow. At the end of three hours all the tissues and fluids examined, except bile, showed little or no penicillin.

*Penicillin in the Treatment of Syphilis*:—Since penicillin has been used in the treatment of syphilis on a considerable scale for only twenty-three months at the date of this writing (Sept. 1, 1945), it is still too early to expect the appearance of any but the most preliminary sort of results. The next two to five years should see them expanded into more definite pronouncements.

After a brief historical review of the chemotherapy of syphilis, Moore [85] describes the nationwide cooperative study of penicillin in syphilis which is in progress under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development and of the National Research Council. Together with the Army, the Navy and the Public Health Service, some twenty-five civilian clinics were invited to participate in a study of the effect of penicillin on early and late syphilis, the results in early syphilis to be pooled and statistically analyzed as a group. In addition, the cooperation of four laboratories was enlisted in order to study in experimentally infected animals the various permutations of the time-dose relationship in both early and late syphilis; to study such other important issues as the effect of penicillin in combination with other chemotherapeutic agents, such as arsenic and bismuth, or in combination with fever, as well as to engage in other important pharmacologic investigations.

The results to the date of the presentation of the preliminary report on this study (October 1944) permit a number of general statements. Several thousand patients with early syphilis had then been treated, but only a few hundred of them had been followed six months or longer. Treatment was by the intramuscular route with injections every three to six hours. The only factor which has so far proved of importance

85. Moore, J. E.: The Chemotherapy of Syphilis, Bull. New York Acad. Med. **21**:3 (Jan.) 1945; Am. J. Syph., Gonor. & Ven. Dis. **29**:185 (March) 1945.

in estimating results is the comparative incidence of relapse, clinical or serologic. With a total dose of 60,000 units in seven and one-half days, the eventual early relapse rate is indicated 100 per cent; with 1,200,000 units, about 15 to 20 per cent. A large series of patients have now been treated with 2,400,000 and 3,600,000 units in seven and one-half days, and are now under observation. The time elapsed is too short to permit definite comparisons. Under simultaneous study is the variable of time. Halving the duration of treatment is not helpful; whether doubling it to e.g., fifteen days improves the situation is a problem for future study. Finally, in early syphilis there is some suggestion that penicillin in combination with an arsenoxide may be more effective than either drug alone. So much for uncomplicated early syphilis. Simultaneously it has been shown that penicillin is apparently completely effective in early syphilis resistant to arsenic and bismuth; it appears to be of great value in the prevention of congenital syphilis in infants born of recently infected mothers; it produces dramatically favorable effects in early neurosyphilis, and it is useful in infantile congenital syphilis. Resistance to penicillin has not been encountered. Late syphilis of various types presents a much more complex problem, which will require many years of study.

As matters stand at present, penicillin is a new and powerful addition to syphilotherapy. How best to use it, alone or in combination with other forms of treatment, is as yet undetermined.

*Early Syphilis.*—Neilson and his associates[86] report preliminary but not particularly informative results of the penicillin treatment of 63 adults and 12 infants (9 with congenital infections) with early syphilis. All of the first group were treated with a total dose of 2,400,000 units of penicillin and were said to have had "adequate" follow-up and observation, although this period of time is not otherwise defined. The results of treatment were good in all but 11 of the 63 adults. In 8 no appreciable fall in serologic titer occurred following treatment; and in 3 patients infectious relapse lesions developed. The initial results in the group of 12 babies and children are described as equally good.

Binkley and Kile[87] were assigned by the Penicillin Panel the following schedules for the treatment of early syphilis positive on dark field examination: (*a*) 1,000 units of penicillin to be given every three

86. Neilson, A. W.; Chard, F. H.; Hanchett, L. J.; Ayers, E.; Stepita, C. T., and Rodriquez, J.: Penicillin in the Treatment of Syphilis and Gonorrhea, South. M. J. **38**:204 (March) 1945.

87. Binkley, G. W., and Kile, R. L.: Rapid Treatment of Early Syphilis with Small Doses of Penicillin: Observations in One Hundred and Fifty-Nine Cases, Arch. Dermat. & Syph. **51**:200 (March) 1945.

hours over seven and one-half days (total dose 60,000 units); (*b*) this same schedule plus oxophenarsine hydrochloride, 40 mg. daily for a total of 320 mg.; (*c*) 5,000 units of penicillin every three hours for a total dose of 300,000 units in seven and one-half days. A total of 159 patients were treated. The relapse rate (all types) in these three series of patients after periods of observation ranging from six to ten months was, respectively: series (*a*), 81 per cent; series (*b*), 60 per cent; series (*c*), 45 per cent. On the other hand, 7 of 10 patients treated with 1,200,000 units in seven and one-half days were clinically and serologically well at the end of one year. The small dosage schedules originally assigned to these workers are obviously inadequate.

Ross and his associates [88] devote considerable space to treatment with penicillin of 5 patients with secondary syphilis, using either 1,200,000 units administered hourly for forty injections in a total of forty hours or 2,400,000 units given every three hours for eighty injections within ten days. The results were unsatisfactory in 3 of the 5 patients.

Norcross [89] has treated 110 patients with primary and 44 with secondary syphilis with the current Army system of 2,400,000 units, given in sixty intramuscular injections of 40,000 units each every three hours in a total of seven and one-half days. The results presented are immediate only, dealing with disappearance of spirochetes and healing of lesions. In these respects, Norcross thinks that the therapeutic response of early syphilis to penicillin is not so rapid as that to oxophenarsine hydrochloride. Incidentally, he also observed that the administration of 1,800,000 to 5,400,000 units of penicillin to 25 non-syphilitic persons did not produce any biologic false positive reactions to serologic tests.

Nelson and Duncan [90] present the immediate result of penicillin treatment of 6 patients with treatment-resistant early syphilis. All the patients had psoriasiform lesions in which, with one exception, T. pallidum was demonstrated by dark field examination. In each instance the lesions had appeared while the patients were under treatment with adequate amounts of trivalent arsenicals, usually combined with bismuth. Varying dosage schedules of penicillin were employed, ranging from a total dose of 60,000 to one of 2,000,000 Oxford units. In all but

88. Ross, A. O. F.; Nelson, R. B.; Lourie, E. M., and Collier, H. O. J.: Treatment of Early Syphilis with Penicillin, Lancet **2**:845 (Dec. 30) 1944.

89. Norcross, B. M.: Observations on Treatment of Early Syphilis with Penicillin, M. Bull. North African Theat. Op. **2**:110 (Nov.) 1944.

90. Nelson, R. A., and Duncan, L.: Penicillin in the Treatment of Early Syphilis Resistant to Arsenic and Bismuth, Am. J. Syph., Gonor. & Ven. Dis. **29**:1 (Jan.) 1945.

1 of the patients the lesions healed promptly, and the serologic trend up to the time of this report was favorable. The mucosal lesions of 1 patient persisted after a total dose of 60,000 units but healed promptly after a subsequent course of 1,200,000 units. On the basis of their experience and the available information to date, the authors recommend a total dosage of not less than 2,400,000 units of penicillin for patients with syphilis resistant to arsenic and bismuth.

McDermott and his co-workers [91] discuss the time-dosage relationship of penicillin therapy as it applies to early syphilis. They summarize as follows:

> Observations of the action of penicillin on infectious syphilis suggest that only short periods of penicillin action are necessary for the immediate destruction of a large number of the organisms, but prolonged penicillin action is necessary for cure. In addition, there is some evidence that *in vivo*, as with bacterial cultures *in vitro*, large increases in the concentration of penicillin for short periods do not shorten this period of time necessary for cure.
>
> Analysis of the regimens under investigation for the treatment of early syphilis reveals that in any given system, regardless of the total amount of penicillin or the number of days of treatment, there is a wide variation in the total period of time during which detectable concentrations of penicillin are present in the serum, depending upon the timing and size of the individual doses.
>
> As both studies *in vitro* and clinical experience lend support to the thesis that *it is not the production of multiple peaks of high concentrations of penicillin but the length of the action at low concentrations which is the important factor,*[92] it is suggested that this penicillin action-time be given consideration in the planning of new regimens for the treatment of syphilis. In calculations involving the use of penicillin in beeswax and other inhibitors of absorption, this time of action of the penicillin is the only available index for comparison with the other systems.
>
> There is a possibility, as indicated by *in vitro* experiments, that once the initial effect of the penicillin action has occurred, subsequent action need not be absolutely continuous to obtain the maximum effect.
>
> Using a serum concentration of 0.078 unit of penicillin as an arbitrary standard, a number of regimens (presented in tabular form) have been calculated which would produce this concentration, for total periods of 90, 120 and 160 hours by a minimum of intramuscular injections.

*Acute Syphilitic Meningitis.*—Nelson and Duncan [93] present a preliminary report of the effect of penicillin on acute syphilitic meningitis in 10 patients. The route of administration was intramuscular. The clinical manifestations in these patients were typical of acute syphilitic meningitis in all, including headache (all patients), stiff neck (3 patients), cranial nerve palsies (5 patients), papilledema (2 patients),

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91. McDermott, W.; Benoit, M., and DuBois, R.: Time-Dose Relationships of Penicillin Therapy: III. Regimens Used in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **29**:345 (May) 1945..

92. The italics are ours. Compare the quotation from Dale in an earlier section.

93. Nelson, R. A., and Duncan, L.: Acute Syphilitic Meningitis Treated with Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **29**:141 (March) 1945.

convulsions, drowsiness and stupor (2 patients); and the laboratory observations were confirmatory. The dose of penicillin employed ranged from 600,000 to 4,000,000 units; the duration of treatment was seven and one-half to eleven days. These dose and time intervals are not suggested as the optimum. The effectiveness of intramuscular treatment in early neurosyphilis and the lack of necessity for use of the intrathecal route are borne out by the results presented.

The patients have been followed for one hundred and four to three hundred and ten days, and no clinical relapses have been observed. The immediate symptomatic result was dramatically favorable in all cases. The effect on the spinal fluid was equally pronounced. The original cell counts before treatment varied from 42 to 1,450. At the last observation, cell counts were normal in 8 of the 10 patients, almost normal in 1 and still considerably elevated (relapse) in 1. The protein content of the spinal fluid likewise showed a definite downward trend. The quantitative Wassermann reaction of the spinal fluid, originally positive in all patients in varying dilutions, has shown improvement in all patients, and reversed to negative in 5 of the 10. The collodial mastic curve has likewise improved. Nelson and Duncan point out that in spite of the observations cited here, it is believed on the basis of the results accumulating in uncomplicated early syphilis, that patients with acute syphilitic meningitis should receive a total of 2,000,000 to 3,000,000 Oxford units of penicillin administered by the intramuscular route every three to four hours day and night, over a minimum period of eight to sixteen days.

Goldman[94] has treated 19 patients with dementia paralytica (18 referred to in the text, 19 in the tables). Eleven of the 18 paretic patients were treated with a combination of intrathecal and intramuscular injections. Six intrathecal injections were given at daily intervals, the first two of 10,000 units and the subsequent four of 20,000 units each, i.e., a total of 100,000 units. In addition, a total of 800,000 units of penicillin was administered intramuscularly during the six days of intrathecal injections. One month later a second series, totaling 1,000,000 units of intramuscular injections alone, was given. Eight patients had fever on one or more days following the intrathecal injection. Pleocytosis in the spinal fluid was observed in "almost every instance." Aside from these, no serious local manifestations from intrathecal treatment were observed. Two of these 11 patients died within ten days following the first series of treatment. Their condition, however, was thought to be very poor before treatment. Of the

94. Goldman, D.: Treatment of Neurosyphilis with Penicillin: A Preliminary Report, J. A. M. A. **128**:274 (May 26) 1945.

remaining 9 patients, 3 are said to have completely recovered, 3 much improved and the remaining 3 somewhat improved.

A second group of patients (7) with dementia paralytica was treated with a combination of artificial fever (the author says three fever sessions given once weekly for a period of four weeks [*sic*] to a total of approximately thirty hours of temperature over 105 F.) and penicillin. After the third or fourth [*sic*] fever treatment, a course of 1,000,000 units of penicillin was given, and a month later another course of 1,000,000 units, without further fever treatment. Of these 7 patients, 2 are said to be completely recovered, 3 much improved and 2 somewhat improved. The author provides no information as to the length of time for which these patients have been followed after treatment and no data as to serologic outcome.

He has also treated 4 patients with tabes dorsalis, 2 of whom had "tabetic crises with pronounced abdominal and other sensory root symptoms." The other 2 had "typical motor manifestations of ataxia of the lower extremities." These 4 patients were treated with penicillin intrathecally only, to a total of 100,000 units given in six daily injections. One of them was subsequently treated with a pentavalent arsenical. The 2 with crises showed "improvement that was almost immediate and is apparently of an enduring nature." There is again no statement as to the length of the observation period, so that "enduring" is perhaps a strong word.

The chief importance of Goldman's paper lies in the fact that he administered a large number of intrathecal injections in doses not exceeding 20,000 units without producing any serious neurologic reactions.

Neymann, Heilbrunn and Youmans,[95] confirming the observations of others that penicillin cannot be demonstrated in the cerebrospinal fluid after its intravenous or intramuscular administration, experimented with the intracisternal administration of the drug to 3 patients. To these 3, single intracisternal injections of 30,000 units each were administered daily for two weeks. Apparently, though one cannot be sure from the cloudy language of the authors, all of these 3 patients had either "acute" or "chronic" reactions, the manifestations of which (headache, "tenseness," muscular twitchings, severe convulsions, stiff neck, pleocytosis, fever, coma) seem to be essentially identical, and 2 of the 3 died ten days after the last intracisternal injection.

These 3 patients apparently form part of a series of 5 patients with dementia paralytica treated by the authors. Eight different methods

95. Neymann, C. A.; Heilbrunn, G., and Youmans, G. P.: Experiments in the Treatment of Dementia Paralytica with Penicillin, J. A. M. A. **128**:433 (June 9) 1945.

of administration of the drug, alone or in combination with other agents, were tried, but it is impossible to determine from the article which method or methods were employed in the individual cases, how much treatment was given or for how long the patients were followed. Three of the 5 patients are dead, 2 from the reactions to treatment described earlier and 1 from "exhaustion," two weeks after treatment. One is improved; the other is unchanged.

The article is worthless as an index of the value of penicillin in neurosyphilis. Its only value lies in the demonstration that the frequent intrathecal injection of such large doses of penicillin as 30,000 to 100,000 units is fraught with great danger.

Emphasizing the local toxicity of penicillin utilized intrathecally, Johnson and Walker [96] report the case of a 22 month old child with an obscure febrile illness of the nervous system, to whom 50,000 units of penicillin was given intraventricularly in 5 cc. of isotonic solution of sodium chloride. One hour later the child went into collapse and was unconscious, with unobtainable blood pressure and with stiffness of the neck. Three hours later a generalized convulsion occurred, which continued with increasing intensity for an hour. Eight hours after the injection, however, the child seemed well. Four days after the first injection, further intraventricular injections were begun, this time with 15,000 units each, and continued twice daily for four additional doses without serious difficulty. This case stimulated Walker and Johnson [97] to further experimental investigation of the possibility of direct damage to the brain by penicillin. The intracortical injection of small amounts of penicillin in cats and monkeys may result in convulsive seizures or death due to circulatory collapse. Powdered penicillin applied locally to the undamaged arachnoid of monkeys, cats and human beings produces clinical and electroencephalographic manifestations of convulsions. On the basis of the reported case and their later animal experimentation, the authors suggest that penicillin should not be used intraventricularly unless absolutely necessary, and then only in small amounts and with caution. This and further similar but as yet unpublished studies are of major importance with respect to the possible intrathecal injection of penicillin by any route (intraventricular, intracisternal, intraspinal) for neurosyphilis.

Hindle and his co-workers [98] report that during investigations on the use of penicillin in neurosyphilis, 28 patients received both penicillin

96. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, J. A. M. A. **127**:217 (Jan. 27) 1945.

97. Walker, A. E., and Johnson, H. C.: The Convulsive Factor in Commercial Penicillin, Arch. Surg. **50**:69 (Feb.) 1945.

*(Footnotes continued on next page)*

and benign tertian malaria. Fifteen of these had penicillin administered simultaneously with the malaria. Hindle and his colleagues demonstrated that penicillin does not suppress fever or the parasite count of active inoculation malaria and that when given before or at the time of the malaria inoculation it does not prevent or postpone the development of fever and parsitemia. This is an advantage to the treatment of neurosyphilis, since both malaria and penicillin can be given simultaneously.

Stokes and his co-workers [99] discuss what is known and what one wants to know regarding penicillin therapy of late syphilis, especially neurosyphilis. Several illustrative cases are presented in this paper.

*Prevention and Treatment of Prenatal Syphilis.*—Lentz and his associates [100] have studied 12 pregnant women with early and 2 with early latent syphilis, and 9 infants with early congenital syphilis, all treated with penicillin. None of these patients had received previous antisyphilitic treatment. The authors conclude as follows:

1. There are several factors in the medical treatment of the syphilitic pregnant woman and the infant with congenital syphilis which are in need of further study and improvement.

2. It was with the thought that some solution to these problems might be found through the use of penicillin that the present study was undertaken. Sodium penicillin exclusively was employed. Experience with the treatment of 14 pregnant women with early syphilis and 9 infants with congenital syphilis formed the basis for this analysis.

3. The material is reported at this time, even though incomplete, since preliminary observations indicate that sodium penicillin has a definitely good effect both on the mother and on the child in syphilis in pregnancy and on infantile congenital syphilis. Because the drug has been released for general distribution, dissemination of even our present limited knowledge seems desirable.

4. The proper total dosage and the time-dose relationship has not been worked out to complete satisfaction either for syphilis and pregnancy or for infantile congenital syphilis.

5. The limited existing data would seem to indicate, however, that total doses of the magnitude of 1,200,000 Oxford units and 2,400,000 Oxford units given intramuscularly round the clock in approximately eight days, as used in the treatment of early syphilis, are well tolerated by the pregnant woman, with the possible

98. Hindle, J. A.; Rose, A. S.; Trevett, L. D., and Prout, C.: The Effect of Penicillin on Inoculation Malaria: A Negative Report, New England J. Med. **232**:133 (Feb. 1) 1945.

99. Stokes, J. H.; Beerman, H.; Ingraham, N. R., Jr.; Lentz, J. W.; Morgan, H. G.; Gammon, G. D.; Steele, W.; Rose, E. K., and György, P.: Penicillin in Late Syphilis: An Interim Report, Am. J. Syph. Gonor. & Ven. Dis. **29**:313 (May) 1945.

100. Lentz, J. W.; Ingraham, N. R., Jr.; Beerman, H., and Stokes, J. H.: Penicillin in the Prevention and Treatment of Congenital Syphilis: Report on Experience with the Treatment of Fourteen Pregnant Women with Early Syphilis and Nine Infants with Congenital Syphilis, J. A. M. A. **126**:408 (Oct. 14) 1944.

exception that therapeutic or placental shock may occur, to be avoided by considerably reducing the dose for the first thirty-six to forty-eight hours of therapy. The course of expert experience with penicillin in syphilis in general suggests the desirability of the higher dosage (2,400,000 Oxford units).

6. Preliminary results indicate that "cure" or suppression of the infection takes place in a number of the mothers and that miscarriage, stillbirth and neonatal death are averted and the infants are born apparently healthy. It must be reiterated, however, that the period of observation for either mother or child has not been long enough to be certain that they have been cured by the dosages employed. The course of the disease has nonetheless been profoundly and favorably affected.

7. Infants with congenital syphilis make a good response to dosage of approximately 18,000 units per pound of body weight. Grossly infected syphilitic infants, however, may be injured by the injudicious use of penicillin. In the present state of our knowledge their treatment should be approached with extreme caution, with reduced dosage and with great emphasis on proper general pediatric care.

Platou and his co-workers [101] present a brief preliminary note concerning 69 infants with manifest early congenital syphilis who have been treated with sodium penicillin by the university groups at Baltimore, Philadelphia, Galveston and New Orleans. Penicillin was administered intramuscularly in isotonic solution of sodium chloride every three hours in sixty injections over a seven and one-half day period. Total doses used ranged from 16,000 to 32,000 Oxford units per kilogram of body weight. No other antisyphilitic treatment was given.

In 34 of these 69 infants reactions occurred during treatment. Nearly all were mild, consisting of moderate fever beginning on the first or second day of treatment and seldom lasting longer than three days. One infant, forty-eight hours after treatment was begun, suddenly had a severe, nearly fatal collapse. Three infants died during or soon after treatment (twenty-four hours, seven days and nine days, respectively, after penicillin was started); all of these had active syphilitic lesions, were under 2 months of age and were in poor general condition. Two other infants died five weeks and fourteen weeks after receiving penicillin; whether the latter deaths were directly or indirectly due to penicillin or syphilis is not known.

In general, the immediate response of early congenital syphilis to penicillin has been gratifying. Cutaneous and mucosal lesion have healed; rhinitis has been somewhat more persistent, healing in from two weeks to two months. Roentgenographic evidence of osteitis disappeared in two to six months. Regression of hepatic, splenic and lymph node enlargement, though variable, was usually complete by three months. If abnormal spinal fluid findings were present initially, these have returned to normal in all cases in from eight days to six months.

101. Platou, R. V.; Hill, A. J.; Ingraham, N. R.; Goodwin, M. S.; Wilkinson, E. E., and Hansen, A. E.: Penicillin in the Treatment of Infantile Congenital Syphilis: A Brief Preliminary Note, J. A. M. A. **127**:582 (March 10) 1945.

Of the 69 infants, 39 have been followed for four to twelve months. Twenty-five of these 39 now are physically normal and show doubtful or negative reactions to serologic tests (21 negative, 4 doubtful). Serologic relapse has occurred in 5 infants, and clinical relapse in 2 of these 5.

The dosage schedules so far employed have corresponded to a total dose of 1,000,000 to 2,000,000 units in seven and one-half days for an adult with early acquired syphilis.

The results obtained to date in infants indicate that the present total dose and time-dose relationship are not entirely satisfactory. For the present, Platou's group believes that an increase in total dose with the same time-dose relationship should be tried first. Accordingly, they recommend temporarily a total dose of 40,000 Oxford units per kilogram of body weight given in sixty intramuscular injections over a seven and one-half day period. Attention is called to the vital necessity of adequate supportive care of acutely ill infants.

*Diffusion of Penicillin Through the Placenta.*—The problem of diffusion of penicillin from the maternal to the fetal circulation was apparently first studied by Herrell, Nichols and Heilman.[102] They administered 100,000 units intravenously to the mother toward the end of the second stage of labor. At delivery or shortly after, blood was obtained from the mother and from the fetal cord for determination of penicillin levels in the blood. The drug was constantly present in the fetal circulation, in concentrations ranging from about one-eighth to one-half of that present in the mother's blood.

This observation has been confirmed by Hutter and Parks[103] and by Greene and Hobby.[104] Hutter and Parks[103] administered penicillin to pregnant women at intervals ranging from twenty-five to one hundred and five minutes before delivery. A dose of 20,000 units to 1 patient and of 40,000 units to 2 patients resulted in concentrations of less than 0.02 unit per cubic centimeter in the infant cord blood. When 100,000 units were administered intramuscularly to the mother, levels ranging from 0.02 to 0.2 units per cubic centimeter were obtained in the fetal cord blood. These concentrations of penicillin are approximately one fifth as great as the concentrations in the maternal blood at the moment of delivery. There are no data on the passage of penicillin through the placenta during the first and second trimesters of pregnancy.

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102. Herrell, W. E.; Nichols, D. R., and Heilman, D. H.: Penicillin: Its Usefulness, Limitations, Diffusion and Detection, with an Analysis of One Hundred and Fifty Cases in Which It Was Employed, J. A. M. A. **125**:1003 (Aug. 12) 1944.

103. Hutter, A. M., and Parks, J.: The Transmission of Penicillin Through the Placenta: A Preliminary Report, Am. J. Obst. & Gynec. **49**:663 (May) 1945.

104. Greene, H. J., and Hobby, G. L.: The Transmission of Penicillin Through the Human Placenta, Proc. Soc. Exper. Biol. & Med. **57**:282 (Nov.) 1944.

Greene and Hobby [104] have also demonstrated the transmission of penicillin through the human placenta. Penicillin was adminstered intravenously to 4 normal patients in active labor. In 2 instances in which the mother received 100,000 units both maternal blood and fetal cord blood showed significant amounts of penicillin within two hours after administration. Another patient received 20,000 units one hour before delivery; penicillin was demonstrated in the maternal but not in the fetal cord blood. In another patient who also received a similar amount of penicillin and who delivered one-half hour later penicillin was demonstrated in the maternal and fetal cord blood but not in the amniotic fluid.

The fact that penicillin passes from the maternal into the fetal circulation in effective concentrations suggests a wide therapeutic application of a relatively nontoxic agent for the control of penicillin-susceptible infections which affect both mother and her unborn infant. Of these infections syphilis should receive greatest consideration.

*The Masking of Syphilis by Small Doses of Penicillin.*—That penicillin administered for the treatment of gonococcal infection might mask or alter the subsequent development of manifestations of concomitantly acquired early syphilis has been generally recognized since Mahoney's discovery of the efficacy of this antibiotic in the treatment of early syphilis. Reports are now beginning to appear substantiating this hypothesis. Ricchiuti [105] presents two such reports. One patient with gonorrhea and balanitis was treated with 100,000 units of penicillin. This was accompanied by an elevation of temperature to 101.4 F., which in restrospect was undoubtedly a Herxheimer reaction. A dorsal slit, subsequently performed, revealed an indurated lesion in the coronal sulcus repeated dark field examinations of which failed to demonstrate T. pallidum. Sixteen days later reactions to serologic tests for syphilis became positive, the penile lesion had healed, and there were not any manifestations of secondary syphilis. A second patient received penicillin (100,000 units) for gonorrhea prior to the development of a penile sore, a time at which specimens appeared persistently free from T. pallidum when subjected to dark field examination. Later, generalized lymphadenopathy occurred, but reactions to blood serologic tests remained negative during an eight week period of observation. The diagnosis of syphilis in this instance could not be made.

Boyd, Wagner and Hewson [106] report the case history of a patient who received 80,000 units of penicillin for gonococcic epididymitis.

105. Ricchiuti, J. F.: Penicillin Therapy in Gonorrhea with Associated Undiagnosed Early Syphilis, U. S. Nav. M. Bull. **43**:1031 (Nov.) 1944.

106. Boyd, G. G.; Wagner, J. A., and Hewson, G. F.: Effects of Subtherapeutic Dose of Penicillin on Development of Primary Syphilitic Lesions, U. S. Nav. M. Bull **43**:1034 (Nov.) 1944.

Sixty days after his last sexual exposure (approximately thirty days after penicillin therapy) a penile lesion developed, which subsequently was proved to be syphilitic. The authors suggest that the penicillin therapy for gonorrhea resulted in a prolonged incubation period for primary syphilis.

Steinberg and Immergut [107] add 3 more case reports to the literature. In the first instance the patient received 125,000 units of penicillin for gonococcal urethritis. Five weeks later, not having been sexually exposed in the interim, the patient reappeared with a genital lesion which was syphilitic on dark field examination. In the second instance the patient received a similar amount of penicillin for gonorrhea. A genital lesion present at that time was inadvertently not subjected to dark field examination until one week later. Repeated dark field examinations then gave negative results for syphilis, as did blood tests, until ten days after the penicillin therapy for gonorrhea. At that time blood tests gave doubtful and later increasingly more positive reactions. The third patient received 125,000 units of penicillin for gonococcic cervicitis. Then and during the subsequent two weeks examinations for syphilis gave negative results. Seven weeks after penicillin therapy the patient returned with a secondary cutaneous rash but with no evidence of a preexisting primary lesion.

Other similar cases have been recorded by Van Slyke and Steinberg,[108] Carpenter,[109] Shafer and Zakon,[110] Hailey,[111] Baier and Pincus [112] and perhaps others, and attention has been drawn to the danger in many papers dealing with the use of penicillin in both gonorrhea and syphilis. The United States Army has dealt with the problem by requiring serologic tests of the blood for syphilis as follow-up after the treatment of gonorrhea with penicillin, the last one not earlier than four months after treatment. This should be sound civilian practice.

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107. Steinberg, S., and Immergut, S.: Diagnosis of Early Syphilis Masked or Delayed by Penicillin Therapy of Gonorrhea, Urol. & Cutan. Rev. **49**:175 (March) 1945.

108. Van Slyke, C. J., and Steinberg, S.: Outpatient Penicillin Treatment of Gonococcic Infections in Males, Ven. Dis. Inform. **25**:229 (Aug.) 1944; Outpatient Penicillin Therapy of Gonorrhea in Men, ibid. **26**:1 (Jan.) 1945.

109. Carpenter, C. C.: Failure of Penicillin to Prevent Syphilis, U. S. Nav. M. Bull. **43**:389 (Aug.) 1944.

110. Shafer, B., and Zakon, S. J.: Early Syphilis Masked and Delayed by Penicillin in the Treatment of Gonorrhea, Arch. Dermat. & Syph. **50**:200 (Sept.) 1944.

111. Hailey, H. E.: Suppression of Syphilis by Penicillin Therapy of Gonorrhea, Arch. Dermat. & Syph. **50**:269 (Oct.) 1944.

112. Baier, G. F., III, and Pincus, J. A.: The Effect of a Small Dose of Penicillin on the Diagnosis of Early Syphilis, Mil. Surgeon **95**:359 (Nov.) 1944.

*Penicillin in Mixed Chancroidal and Syphilitic Infections.*—Pereyra and Landy [113] point out that penicillin is ineffective in the treatment of chancroidal infections in man, a point of importance in mixed infections with chancroid and syphilis. Failure of a chancre to heal under treatment with penicillin may occur under these conditions, and supplementary treatment with sulfonamide drugs may be necessary.

*Asthma as a Reaction to Penicillin.*—Price and his associates [114] report a serious reaction occurring in a white man, aged 24, with early syphilis, to whom was given 2,400,000 units of penicillin divided into sixty doses of 40,000 units each, administered intramuscularly every three hours in seven and one-half days. Two days after the completion of this treatment asthma, giant urticaria, fever and malaise developed. There was a remarkable association between the height of the fever and the intensity of urticaria and asthma. Three days after the onset of this reaction the patient had a very severe asthmatic attack in which he became comatose and his rectal temperature rose to 105 F. The entire episode ended in four to five days in complete recovery. Sensitivity of the skin to penicillin could not be demonstrated in this patient.

*New Books Dealing with Penicillin in Syphilis.*—The third edition of "Modern Clinical Syphilology," now for the first time under the joint authorship of Stokes, Beerman and Ingraham,[115] has just appeared. It is, as it has been in the two preceding editions, the outstanding contribution in English or in any other language in the general field of syphilology. The final chapter is devoted to penicillin. It is inescapable that at this time many of the statements in this chapter must be regarded as provisional, subject to immediate and perhaps drastic revision. For a statement of current knowledge as of the time of writing (September 1944), and particularly the gaps in present knowledge, it cannot be too highly commended. Figures 897 (A General Statement of Facts) and 898 (The Known and the Unknown) from this text provide in brief form an excellent summary of knowledge about the use of penicillin in cases of syphilis as of the late summer of 1944.

Herrell's [116] three hundred and forty-eight page monograph, "Penicillin and Other Antibiotic Agents," provides a useful general summary

113. Pereyra, A., and Landy, S.: Experimental Prophylaxis and Treatment of Chancroidal Infection: Inefficacy of Penicillin Administered Intramuscularly, U. S. Nav. M. Bull. **43**:189 (July) 1944.

114. Price, D. E.; McNairy, D. J., and White, E. L.: Severe Asthma: Delayed Sensitization to Penicillin, J. A. M. A. **128**:183 (May 19) 1945.

115. Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Modern Clinical Syphilology, ed. 3, Philadelphia, W. B. Saunders Company, 1944.

116. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1945.

of the present status of penicillin. Of special interest to the syphilotherapeutist are the chapters on the physical and chemical properties of the drug; on its absorption, diffusion and excretion and on its clinical use in syphilis (Chapter XVII). The last-named chapter includes a summary of the scanty available literature (to April 1945). The criticism may be offered that definite plans of treatment for various stages of syphilis are proposed, though there is as yet no definite evidence that the plans suggested are of maximum effectiveness or even that at least one of them (e. g., for neurosyphilis, 20,000 units of penicillin administered intrathecally every forty-eight hours during the period of systemic therapy) is safe. Although the absorption-delaying method of administration of penicillin in peanut oil–beeswax (Romansky and Rittman) is described, its possible applicability in the treatment of syphilis is not discussed.

Kolmer [117] has likewise summarized available current knowledge concerning penicillin in a small monographic presentation of three hundred and two pages. This book also includes the basic information on the physical and chemical properties of the drug, its action and toxicity, the administration of a dosage and a twenty page chapter on the use of the drug in syphilis. Kolmer, recognizing the preliminary nature of the so far published information, refrains from offering definite plans of treatment for various types of syphilis, contenting himself with a careful review of the reports of others.

## CARDIOVASCULAR SYPHILIS

*Incidence.*—An excellent opportunity to determine the incidence of cardiovascular syphilis in the younger age group has been afforded by selective service examinations. Flaxman [118] recorded the incidence of cardiac history and findings among 23,000 inductees and volunteers examined in Chicago from February 1943 to June 1944. Of the entire group, only 3 were found to have syphilitic aortic insufficiency. There is no recorded incidence of an aneurysm; uncomplicated syphilitic aortitis was unmentioned. Therefore only 0.0013 per cent of the entire group were found by Flaxman to have syphilitic heart disease. There were 203 (12.4 per cent of the men with a history of the physical findings of cardiac disease) with rheumatic heart disease, and it is of interest to note that 15 of these (7.4 per cent) had rheumatic lesions of the aortic valve only.

117. Kolmer, J. A.: Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy, New York, D. Appleton-Century Company, Inc., 1945.

118. Flaxman, N.: Initial Cardiac Examination of Twenty-Three Thousand Inductees and Volunteers, Am. J. M. Sc. **209**:657 (May) 1945.

*Syphilitic Aortitis.*—Jackman and Lubert[119] think that syphilitic aortitis is a much more frequent cause of calcification in the aortic wall than is aortic atherosclerosis. This opinion is based on roentgenographic evidence of aortic calcification in 22.7 per cent of 66 patients, averaging 57 years in age, subsequently proved to have syphilitic aortitis, as contrasted with similar roentgenographic evidence in only 3.2 per cent of 62 patients, averaging 70 years in age, with anatomically proved cases of severe sclerosis of the thoracic aorta. On the other hand, Blumenthal, Lansing and Wheeler,[120] who studied pathologic sections from 582 aortas, think that age and hypertension are more important factors than syphilis in the production of calcium deposits.

*Differential Arterial Blood Pressure in Aortic Regurgitation.*—The commonly used clinical methods of measuring arterial blood pressure are based on the concepts proposed by the original workers, remark Kotte, Iglauer and McGuire.[121] Examination of these early publications reveals that their technics are founded on indirect evidence. The usual clinical concept is that the femoral systolic blood pressure is approximately equal to that in the brachial artery in normal persons but that in aortic insufficiency and under certain other conditions it is considerably higher.

In the present study blood pressure was measured in the brachial and femoral arteries of subjects with normal pressures, hypertension and aortic insufficiency by cuff methods and by use of the direct method (a small needle is inserted into the artery and blood pressure readings are measured by a specially designed instrument, an optical manometer). It was desired, first, to test the accuracy of the 15 cm. cuff for measurements of blood pressure in the thigh; second, to test the validity of the impression that aortic regurgitation produces a disproportionate elevation of the systolic pressure in the leg, and, third, to compare the respective femoral pressures with the concomitant pressures in the arms.

Measurements were made on 9 patients with normal blood pressures, 9 with hypertensive cardiovascular disease and 10 with aortic insufficiency. The ordinary arm cuff (13 cm. in width) was used for the arm, and the same cuff and, in addition, a wider cuff (15.5 cm.) were used for

119. Jackman, J., and Lubert, M.: The Significance of Calcification in the Ascending Aorta as Observed Roentgenologically, Am. J. Roentgenol. **53**:432 (May) 1945.

120. Blumenthal, H. T.; Lansing, A. I., and Wheeler, P. A.: Calcification of the Media of the Human Aorta and Its Relation to Intimal Arteriosclerosis, Ageing and Disease, Am. J. Path. **20**:665 (July) 1944.

121. Kotte, J. H.; Iglauer, A., and McGuire, J.: Measurements of Arterial Blood Pressure in the Arm and Leg: Comparison of Sphygmomanometric and Direct Intra-Arterial Pressures, with Special Attention to Their Relationship in Aortic Regurgitation, Am. Heart J. **28**:476 (Oct.) 1944.

measurements of the femoral pressures. The cuff pressures in the arm varied both above and below the direct values. The error was slight for the systolic level, averaging + 0.5 per cent, but reached more sizable proportions with the diastolic pressures of the normotensive and hypertensive groups, in which it was of the order of + 9 per cent. The cuff error for diastotic pressures was even greater in subjects with aortic regurgitation, averaging + 24 per cent. The 15.5 cm. cuff permitted a much more accurate measurement of the femoral pressures than did the 13 cm. cuff. With the 15.5 cm. cuff the average error in the normotensive and hypertensive groups was + 2.6 per cent and + 8 per cent, respectively. In this instance the error in the results for the diastolic pressure averaged + 25 per cent for the combined groups. The systolic and diastolic values with the wide cuff on the thigh were most in error in subjects with aortic regurgitation (averaging + 29 per cent and + 67 per cent, respectively). The femoral systolic blood pressure was notably higher than the direct brachial systolic pressure in 5 of the 9 normotensive subjects, 4 of the 9 hypertensive and 7 of the 10 patients with aortic regurgitation. It is pointed out that the femoral systolic pressure was more frequently elevated in the patients with aortic regurgitation and that the differences were usually greater in these subjects than in the control and hypertensive groups.

Kotte and his colleagues conclude that the systolic blood pressure in the arm can be measured with reasonable accuracy in subjects with normal pressure, hypertension and aortic regurgitation by the ordinary arm cuff and auscultatory technic. The brachial diastolic pressure as measured by the cuff is usually too high, especially in aortic regurgitation. The femoral systolic blood pressure cannot be measured accurately with the 13 cm. cuff, but the 15.5 cm. cuff permits more accurate measurements in all except subjects with aortic regurgitation, whose pressures cannot be measured accurately with either cuff. Femoral diastolic pressures obtained with either cuff were grossly inaccurate in all subjects.

Finally, the difference between the blood pressure in the arm and that in the leg in patients with aortic regurgitation is not so pronounced as is generally believed because the cuff, wide or narrow, does not allow true measurements of femoral pressure. Therefore it is probable that no diagnostic value should be attributed to the differential blood pressure.

*Abdominal Aneurysms.*—The overwhelming role of syphilis in the causation of aneurysms of the thoracic aorta has been repeatedly and conclusively demonstrated. Aneurysms of the abdominal aorta have been less thoroughly studied. Scott [122] finds that, although more than

122. Scott, V.: Abdominal Aneurysms: A Report of Ninety-Six Cases, Am. J. Syph., Gonor. & Ven. Dis. **28**:682 (Nov.) 1944.

500 cases are reported in the literature, many publications antedate both the discovery of the Wassermann reaction and the general recognition of the specific histopathology of syphilitic aortitis. He summarizes his own study as follows:

1. The etiology of abdominal aneurysm (aorta and branches) in 96 patients was as follows: syphilis 58.3 per cent, arteriosclerosis 20.0 per cent, bacterial agents (mycotic) 18.8 per cent, periarteritis nodosa 1.0 per cent, and tuberculosis by direct extension 1 per cent.

2. Sixty-two patients had aneurysms of the abdominal aorta of which 74 per cent were syphilitic, 21 per cent arteriosclerotic, and 5 per cent mycotic.

3. Of 43 patients with aneurysms of branches of the abdominal aorta, 35 per cent were due to syphilis, 18.6 per cent to arteriosclerosis, 41.9 per cent to bacterial agents. Tuberculosis and periarteritis caused aneurysm in one patient each.

4. Multiple abdominal aneurysms were present in 18.7 per cent of the patients (14.4 per cent of the syphilitic group, 30 per cent of the arteriosclerotic, 16.5 per cent of the mycotic).

5. Syphilis is the major cause of aneurysms of the upper abdominal aorta and of aneurysms arising at the origin of the major upper branches (celiac axis and superior mesenteric artery). Aneurysms of the lower aorta and of other branches are rarely syphilitic; instead, they are arteriosclerotic (aorta), or mycotic (smaller branches).

6. Of the syphilitic aneurysms, 75 per cent occurred in patients under 50 years of age, and 98 per cent under age 60. All the arteriosclerotic aneurysms occurred in patients over 50, and 70 per cent were in the age group over 60. The highest incidence of mycotic aneurysms was in the younger age groups.

7. The incidence of syphilitic aneurysms was highest in the colored race (64 per cent) and in the male sex (89 per cent). Arteriosclerotic aneurysms in this series were limited to patients of the white race and 85 per cent occurred in males.

8. The symptomatology of abdominal aneurysm is variable because of differences in location and size. In the syphilitic group the most significant symptom was pain (abdominal or back) present in 84 per cent. This was characteristically most severe at night and relieved by change of position. The majority (80 per cent) of arteriosclerotic aneurysms were asymptomatic.

9. The presence or absence of the characteristic physical manifestations of abdominal aneurysm—a mass exhibiting an expansile pulsation, a palpable thrill, and an audible bruit—is again related to site and size. Of these, the former was most constantly present (75 per cent) in the syphilitic group.

10. Contrary to previous reports, the patients in this series with syphilitic abdominal aneurysms showed a high incidence of syphilitic involvement of the thoracic aorta and of the aortic leaflets—34 per cent had saccular thoracic aneurysms and an additional 18 per cent syphilitic aortic regurgitation.

11. The important roentgenologic findings are: (1) erosion of the vertebral column resulting from pressure of the aneurysm, the vertebrae commonly involved being the eleventh dorsal through the second lumbar, and (2) the presence of calcium deposits in the wall of the aneurysmal mass.

12. The prognosis of syphilitic abdominal aneurysm, though usually grave, may be quite variable. Although 70 per cent succumbed within 36 months after onset of symptoms, 17 per cent survived more than 5 years.

13. The case history of one patient who has survived for 28 years is reported.

Epstein [123] reviews most of the literature pertaining to abdominal aneurysms and adds 9 additional cases.

Lazarus and Marks [124] discuss abdominal aortic aneurysm in its relationship to urologic manifestations and record a case of this type presenting urinary symptoms. The possible effects of an upper abdominal aortic aneurysm on the kidneys may be due to changes in the local circulation, direct pressure on the kidney itself or interference with renal drainage. Should the aneurysm be situated above the origin of the renal arteries, one or both will eventually suffer from reduced flow of blood. However, a lesion situated below the origin of the renal arteries may eventually lead to dilatation of these arteries with resultant hyperemia of the kidneys, with the presence of occult blood in the urine. The pain of abdominal aortic aneurysm often simulates renal colic. The most frequent roentgenologic observations are of renal or ureteral displacement and osseous erosion. Lateral roentgenograms are of invaluable aid in demonstrating these conditions, and roentgenograms should be carefully searched for calcareous shadows adjacent to the renal silhouette.

The same authors [125] review the literature and report a case of aneurysm of the renal artery. In only 3 of 75 reported cases was syphilis mentioned as an etiologic factor. A history of trauma was elicited in 34.7 per cent of the reported cases. Other etiologic factors were atherosclerosis and systemic debilitating infections. Small aneurysms of the renal artery usually give rise to no symptoms. Larger aneurysms, however, usually produce symptoms the most common of which is pain in the loin (62.7 per cent). A mass was felt in the loin in 30 per cent of the recorded cases. The presence of an opaque ring shadow with dense periphery on the roentgenogram in the region of the renal pelvis is a valuable diagnostic sign. The indicated procedure in the treatment of aneurysm of the renal artery is immediate nephrectomy with ligation of the renal artery proximal to the point of origin of the aneurysm.

### NEUROSYPHILIS

*Incidence.*—Of 218,133 selectees passing through the Armed Forces Induction Station, New York city, Guidotti and his co-workers [126] found

123. Epstein, J.: Aneurysms of the Abdominal Aorta, Ann. Int. Med. **22**:252 (Feb.) 1945.

124. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Abdominal Aorta Associated with Urinary Symptoms, J. Urol. **52**:115 (Aug.) 1944.

125. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Renal Artery—True and False—with Special Reference to Preoperative Diagnosis, J. Urol. **52**:199 (Sept.) 1944.

5,587 to have syphilis, the prevalence by race being 1.03 per cent for white persons and 12.16 per cent for Negroes. This study is particularly concerned with the results of examinations of the spinal fluid of 3,000 of the syphilitic selectees. "Sufficient pathologic changes to cause rejection" were found in 294 (9.5 per cent), all but 15 of whom had positive reactions to Wassermann tests of the spinal fluid.

Data on 1,176 blind persons receiving aid for the blind in Massachusetts have been coded in accordance with the standard classification developed by the Committee on Statistics of the Blind. Riemer [127] presents these data in tabular form, classifying the cases according to topography and type of disease, etiology and age at onset of blindness. In 128 cases (about 11 per cent of the whole number) blindness was due to syphilis, and in 101 of these it was due to syphilis acquired after birth. Twelve per cent of all blindness was due to atrophy of the optic nerve, and only 1.3 per cent to interstitial keratitis.

*Syphilis of the Spinal Cord.*—Adams and Merritt [128] present a valuable discussion of syphilis of the spinal cord. They describe the anatomic and physiologic considerations of the several forms of the disease, which they classify in four groups: (*a*) syphilitic meningomyelitis, which includes amyotrophic meningomyelitis, syphilitic spastic paraplegia, amyotrophic syphilitic myelitis and systematized spinal sclerosis; (*b*) spinal vascular syphilis; (*c*) syphilitic spinal pachymeningitis, including gumma of the spinal cord and syphilitic hypertrophic pachymeningitis, and (*d*) syphilitic poliomyelitis. Cases typical of the various clinical entities are briefly presented.

*Tabes Dorsalis.*—In a previous review,[1E] attention has been called to the similarity between the lesions of tabes dorsalis and those produced experimentally in pigs on vitamin-deficient diets.

Follis and Wintrobe [129] report from their laboratory further experiments on swine in which deficiencies in vitamins of the B complex have been produced. Of particular interest have been the studies on the relationship of vitamin deficiency to the integrity of nervous tissues. It was first shown that degeneration of the peripheral nerves, dorsal root

126. Guidotti, F. P.; Carrier, R. N., and Stumpf, W. E.: Spinal Fluid Findings in Cases of Syphilis in the General Population of Males Between the Ages of Eighteen and Thirty-Eight Years Without Detectable Neurologic Changes, New York State J. Med. **44**:2488 (Nov. 15) 1944.

127. Riemer, H. B. C.: Topographic and Etiologic Study of 1,176 Indigent Blind Persons in Massachusetts: A Basis for Prevention of Blindness, Arch. Ophth. **32**:304 (Oct.) 1944.

128. Adams, R. D., and Merritt, H. H.: Meningeal and Vascular Syphilis of the Spinal Cord, Medicine **23**:181 (May) 1944.

129. Follis, R. H., Jr., and Wintrobe, M. M.: A Comparison of the Effects of Pyridoxine and Pantothenic Acid Deficiencies on the Nervous Tissues of Swine, J. Exper. Med. **81**:539 (June 1) 1945.

ganglion cells and posterior columns of the spinal cord should be produced when young swine were fed a basal diet (crude casein, sugar, lard, salts and cod liver oil) supplemented only with crystalline thiamine hydrochloride and riboflavin. Although the inclusion of nicotinic acid in this diet led to some improvement in growth of the animals, changes in the nerves, ganglion cells, and spinal cord continued to appear. When other vitamins of the B group became available, it was shown that good growth could be obtained and neural lesions could be prevented if choline, pyridoxine and pantothenic acid were added to the basal diet already supplemented with thiamine, riboflavin and nicotinic acid. Finally, it was established that lesions could be produced in sensory neurons when pyridoxine and/or pantothenic acid was excluded from the diet.

The experiments here reported were undertaken to compare the effects of a deficiency of pyridoxine and pantothenic acid on the nervous tissues of swine. The demonstration that these vitamins may have specific actions on sensory neurons has obvious implications for some of the fundamental problems of neurophysiology and neuropathology. Follis and Wintrobe say:

> Observations were made on 2 separate groups, totalling 45 swine of both sexes. One group (series I) was placed on the deficient diet at about 32 days of age, the other (series II) at about 20 days of age. . . .
>
> When the pigs were received in the laboratory they were placed on the basal diet: Sheffield "new process" casein, 26.1 per cent; sucrose, 57.7 per cent; lard, 11 per cent; salt mixture, 5.2 per cent, and Mead's blended oil. Brewers' yeast was given until the experimental deficiency was begun, at which time crystalline vitamins were administered daily in the following amounts per kilo: thiamin hydrochloride, 0.52 mg.; riboflavin, 0.13 mg.; nicotinic acid, 1.20 mg.; choline chloride, 10.0 mg.; inositol, 0.1 mg. (series II) and para-aminobenzoic acid, 0.1 mg. (series II). Varying amounts of pyridoxine and/or calcium pantothenate were administered.

As the pigs died or were killed autopsies were performed as promptly as possible.

> These experiments confirm previous studies from this laboratory and show that diets containing inadequate amounts of pyridoxine or pantothenic acid or both lead to degeneration of the sensory neurons of swine. A different morphological pattern has been observed in the two groups, however, especially when the pathogenesis of the lesions was studied during the early stages. Myelin degeneration of the peripheral portion of the sensory nerve appeared to be the initial change in pyridoxine-deficient animals. Axis cylinder degeneration almost immediately became apparent as well. Chromatolysis of the dorsal root ganglion cells was extremely inconspicuous, either early or late in the course of the deficiency. Atrophy, followed by necrosis and neuronophagia, was observed without supervening chromatolytic phenomena. In contrast, the initial morphological change found in animals whose diet was deficient in pantothenic acid has been pronounced chromatolysis of the dorsal root ganglion cells. Atrophy of these cells was not prominent. Only later could evidence of myelin and axis cylinder degeneration be detected in

the peripheral nerves and dorsal roots where it was never as extensive as that observed in the pyridoxine-deficient pigs. The nervous tissues of animals deficient in both vitamins revealed changes similar to those found when pyridoxine or pantothenic acid deficiency was present alone. . . .

The morphological changes described in this report would seem to indicate that the primary site of injury to the neuron in pyridoxine-deficient animals is in its peripheral process (myelin sheath and axon). In contrast, the initial locus of damage in pantothenic acid—deficient animals would seem to be in the cell body itself. It must clearly be borne in mind that such a conclusion is based entirely on morphological data. However, the hypothesis is an intriguing one and helps explain the differences in the pathologic pictures. Moreover, it has a basis of fact if the pathogenesis of some common neurological disease is considered.

The "primary" diseases of the nervous system can be divided pathologically into two types: myelinoclastic and polioclastic. . . .

The course of the degeneration of the nerve fibers was not specifically studied in these experiments. However, since degeneration of the sensory nerve roots and dorsal columns was not seen in animals deficient in either vitamin unless well marked changes were found in the peripheral nerves, it would seem that the latter, especially in pyridoxine deficiency, are the most vulnerable. . . .

Attention must be called to the changes in the spinal ganglion cells in a few of the animals deficient in pantothenic acid. Such lesions were not found in pyridoxine-deficient swine. These changes may further indicate that pantothenic acid plays a more important rôle than pyridoxine in the metabolism of the perikaryon. . . .

. . . the gait of the two groups of animals differed. Whereas pyridoxine-deficient animals showed a swaying and twisting of the legs as an early sign, those deficient in pantothenic acid rarely showed this symptom, but would lift one leg suddenly off the ground as though it were painful. . . . The onset of ataxia and the development of pathological lesions were earlier in the animals deficient in pantothenic acid. There was little difference, however, between the late manifestations in the two groups of animals. . . .

In view of the common acceptance of thiamin as "the antineuritic vitamin" it would seem worthwhile to mention that we have failed to produce lesions of the nerves in swine deficient in this vitamin.

Emmett [130] classifies the tabetic bladder as a "pseudo-cord bladder." He states that although it is true that tabes dorsalis may play a role in vesical dysfunction and urine retention, this role is one of minor importance. The part played by tabes dorsalis is only one of reduction in sensation, due to sensory disturbances of the posterior roots of the spinal nerves and of the posterior columns of the spinal cord. This delays normal reflex stimuli from reaching the bladder and the normal desire of micturition from reaching the threshold of consciousness until the bladder is more distended than normally. The final result over a long period is a distended, weakened bladder that is unable to expel its contents completely through a moderately obstructed vesical neck. As nearly all patients who have this type of vesical dysfunction are more than

130. Emmett, J. L.: Transurethral Resection in Treatment of True and Pseudo Cord Bladder, J. Urol. **53**:545 (April) 1945.

40 years of age, the incidence of some form of obstruction is high. In nearly all these cases transurethral resection of the vesical neck will permit the patients to empty their bladders completely. The author believes that syphilis of the central nervous system (including tabes dorsalis) is not the important etiologic factor in urinary retention that it previously was thought to be.

*Treatment.*—(*a*) General: Solomon and his associates [131] outline briefly, for the benefit of Army physicians, the latest present day suggestions for the treatment of neurosyphilis. Outlines of treatment are recommended for the various forms of neurosyphilis to secure "the maximum benefit of treatment which can be secured by hospitalization in a general hospital not to exceed 3 months."

(*b*) Charcot Joint: In an article concerned primarily with treatment of the tabetic arthropathies, Key [132] lays special stress on early diagnosis. He believes that in the initial stages of Charcot's disease the involved joint first passes through an acute or progressive stage during which the tissues of the joint tend to disintegrate rapidly and are especially vulnerable to even mild injury. This is followed by a stage during which the swelling tends to subside, the excess synovial fluid to be absorbed and the bones and ligaments to toughen. Key advises complete rest for the early Charcot joint, preferably with the patient in bed. After the initial period of rest in bed the patient is allowed to resume weight bearing with as much protection as can be provided. In the treatment of the late stages of Charcot's joints conservative treatment is preferred to operative procedures.

(*c*) Complications of Fever Therapy: Jaundice is mentioned as a rare complication of artificial fever, occurring only in cases in which there is definite circulatory collapse or dehydration or in which the level of the blood chlorides is low. Contrary to this usual experience, MacDonald [133] has encountered 48 cases of jaundice in 250 patients treated with fever for sulfonamide resistant gonorrhea. In the twelve hours preceding fever therapy, the patients were given 6 Gm. of sulfathiazole or sulfadiazine. Treatment consisted of the maintenance of a temperature above 106 F. for seven hours. Clinical icterus was usually detected on the second or third day after fever. Five patients had extreme, 6 moderate and the remaining 37 mild icterus. Only 2 patients were

131. Solomon, H. C.; Moore, J. E.; O'Leary, P. A.; Stokes, J. H., and Thomas, E. W.: The Treatment of Neurosyphilis, Bull. U. S. Army M. Dept., November 1944, no. 82, p. 66.

132. Key, J. A.: The Treatment of Tabetic Arthropathies, Urol. & Cutan. Rev. **49**:161 (March) 1945.

133. MacDonald, R. M.: Toxic Hepatitis in Fever Therapy, Canad. M. A. J. **51**:445 (Nov.) 1944.

critically ill, and there were no fatalities. The author suggests that the high incidence of icterus in the present series may result from the effect of fever on a body with a relatively high blood level of sulfonamide drug. The possibility of infectious hepatitis does not seem to have been excluded.

Fredricks and Hoffbauer [134] have evaluated hepatic function in 31 neurosyphilitic patients given therapeutic benign tertian malaria. The criterion for a complete course of malaria was considered to be either forty hours of fever at or over 103 F. or one hundred and fifty hours of fever with the oral temperature at or over 100 F. The 31 patients included in the investigation were divided into two groups. The first 20 were given general diets. Because of the consistent hepatic disturbance observed, the use of liver-sparing diets (high carbohydrate, high protein and low fat) was added to the study. The last 11 patients were given alternately the special and the general hospital diet.

The hepatic disturbance resulting was evaluated by (1) the quantitative serum bilirubin test, (2) the cephalin-cholesterol flocculation test, (3) the amount of urobilinogen in a twenty-four hour sample of the urine and the two hour quantitative Ehrlich reaction of the urine and (4) the sulfobromophthalein sodium dye retention test. Quantitative serum bilirubin determinations were performed on all 31 patients. Twenty-four of the 29 patients studied adequately showed an increase in total bilirubin during the malarial fever. Elevations to 1.7 mg. or more of prompt direct reacting bilirubin per hundred cubic centimeters were considered significant and were observed in 8 cases. Six of the patients were receiving the "general diet," and 2 the special diet. Eighteen "general diet" patients and 6 "special diet" patients showed significant and comparable increases in their reactions to the cephalin flocculation test. Of 13 "general diet" patients significant increases of urobilinogen in the urine were noted in 9. The remaining 4 were not tested prior to malarial therapy, but 3 showed excessive excretion of urobilinogen in the course of their treatment. Eleven patients, 5 of whom were "general diet" and 6 "special diet" patients, were tested by the two hour Ehrlich method. Nine of the 11 showed significant increase in excretion of urobilinogen. There was no appreciable difference between the general and special diet groups. Retention of sulfobromophthalein sodium was tested in 8 patients before as well as during and immediately after therapy. Five of the 8 showed significant increases. However, in 3 patients retention of dye decreased in the course of their therapy. Again there was no appreciable difference between the general and special diet groups.

134. Fredricks, M. G., and Hoffbauer, F. W.: A Study of Hepatic Function in Therapeutic Malaria, J. A. M. A. **128**:495 (June 16) 1945.

Fredricks and Hoffbauer say that more attention should be given to the use of liver-protective diets in therapeutic malaria. They feel that malarial therapy is contraindicated in the presence of clinically manifest hepatic disease (as, for example, cirrhosis). The use of tests of hepatic function before fever malarial therapy is advised.

Careful studies on the blood-clotting mechanism during the course of therapeutic malaria for neurosyphilis are reported by Diggs.[135] The platelet count, bleeding time, coagulation time, clot retraction time, extracorpuscular volume, capillary fragility and prothrombin concentrations were determined at weekly intervals for 40 white patients receiving Plasmodium vivax malaria, for 9 white patients with Plasmodium malariae malaria, and for 10 Negroes with Plasmodium falciparum malaria. The noteworthy observation was that thrombopenia developed in all patients during the febrile period. Although the fall in blood platelets varied according to the method of determination, the decrease in platelet count was approximately one half to one third of the preinoculation values. Platelet counts made by means of the indirect method of MacKay were usually within the range of 150,000 to 300,000 per cubic millimeter during the febrile period. With the direct Rees-Ecker method and with the indirect moist brilliant cresyl blue method platelet counts were often less than 100,000 per cubic millimeter, and in some patients less than 25,000 per cubic millimeter. The platelet counts did not significantly change during individual paroxysms and soon after termination of malarial therapy returned to normal preinoculation values. This important observation may explain some of the hemorrhagic reactions (purpura, epistaxis and vaginal bleeding) sometimes encountered in the course of therapeutic malaria.

(*d*) Electric Shock Therapy: Since Feb. 4, 1943, 34 patients with dementia paralytica have been treated with electric shock by Petersen[136] at the Rochester (N. Y.) State Hospital. Curare was used in conjunction with the treatment in 18 cases. Thirty of the patients were men and 4 were women. The ages ranged from 28 to 60 years. The number of shocks administered to a patient varied from two to thirty-seven. A total of five hundred and thirty-eight treatments were given to the entire group. The current used in the initial treatment in each case was 500 milliamperes applied for 0.2 second. If a convulsion was not induced, the current was increased by steps up to 650 milliamperes.

135. Diggs, L. W.: Platelet Count, Bleeding Time, Clotting Time, Capillary Fragility, Prothrombin Concentration and Clot Retraction in Paretics Receiving Therapeutic Malaria, Am. J. Clin. Path. **14**:534 (Oct.) 1944.

136. Petersen, M. D.: Electric Shock in the Treatment of Dementia Paralytica, Proc. Staff Meet., Mayo Clin. **20**:107 (April 4) 1945.

which is near the maximal output of the apparatus. If a seizure was not induced by this current, the time of application was lengthened.

Of the 34 patients treated, 20 showed great, 9 slight and 5 no improvements. Four of those showing slight improvement had a relapse, but there was improvement again after a second series of electric shock. Thirteen of the patients had previously received fever therapy, and 21 had not. Since there was considerable difference in the two groups and the number is small, no valid conclusions can be drawn from statistical comparison. The best response was obtained in the agitated group. Improvement in the cerebrospinal fluid was noted in the majority of 16 patients who had not previously been treated with fever therapy.

(*e*) Lumbar Puncture Headaches: Levin [137] has analyzed, from the standpoint of headaches, the results of lumbar punctures performed during a five and one-half month period on 2,217 syphilitic candidates for induction into the armed forces. The fluids were collected rapidly; the patients got on their feet immediately and were instructed to keep active and not to lie down. Only 15 cases of postpuncture headache severe enough to require rest in bed were reported. The patients responded to from one to three days of rest in bed and liquid diet. The rapid collection of spinal fluid and the maintenance of the erect position following puncture apparently decreased the number of postspinal headaches to less than 1 per cent. This is believed to be due to the more nearly normal intracranial pressure maintained by the erect position, preventing oversecretion and compensatory intracranial hypertension with resultant headache.

### SYPHILIS AND PREGNANCY

*Incidence in Australia.*—Hughes's [138] study, based on the routine Wassermann and Kahn tests performed on 28,924 pregnant women, demonstrated that 160 (0.55 per cent) had a positive serologic reaction for syphilis. As this is the largest series yet published in Australia, it is a fair indication of the incidence of syphilis in pregnant women attending hospital antepartum clinics in that country.

*Treatment.*—The treatment of the antepartum patient with early infectious syphilis has always been a problem. The patient frequently presents herself for the first time so late in pregnancy that it is difficult to give her sufficient treatment. At Bellevue Hospital Speiser and his

137. Levin, M. J.: Lumbar Puncture Headaches, Bull. U. S. Army M. Dept., November 1944, no. 82, p. 107.

138. Hughes, T. D.: Syphilis in Pregnant Women: A Study Based on the Routine Wassermann and Kahn Tests Performed on 28,924 Patients, M. J. Australia **2**:273 (Sept. 9) 1944.

co-workers [139] adopted massive arsenotherapy for patients with early infectious syphilis and decided to give the same type of treatment to antepartum patients with early syphilis. Thirty-six pregnant patients with early infectious syphilis were treated. In this group the syphilitic lesions appeared in 16 during the first trimester, in 13 during the second and in 7 during the last trimester of pregnancy. In addition, 5 patients with early latent syphilis and 2 with late latent syphilis were treated.

Of the 43 pregnant patients treated, 6 received oxophenarsine hydrochloride alone; 1 patient received 1.2 Gm. of oxophenarsine hydrochloride in six days; 1, 0.88 Gm. in nine days; 3, 0.84 Gm. in six days, and 1, 0.72 Gm. in six days, depending on the dosage in vogue at the time. Eight patients received from 0.6 to 0.8 Gm. of oxophenarsine hydrochloride and two to three (typhoid vaccine) bouts of fever in seven to eight days. Twenty-nine patients were placed on the ten day plan of treatment finally adopted, with 0.5 to 0.6 Gm. of oxophenarsine hydrochloride and three to four bouts of fever in the ten day period. Twenty-three of these patients also received bismuth.

In the fever-treated group, vomiting frequently followed the first few injections of exophenarsine hydrochloride. In only 1 instance did a patient continue vomiting through the entire course of oxophenarsine therapy. One patient had erythema on the ninth day. In 3 patients epistaxis was encountered. There were no instances of jaundice, granulocytopenia or peripheral neuritis. Unfortunately, in the last patient treated arsenical encephalopathy developed, and the patient died after the fifth injection of 0.07 Gm. of oxophenarsine hydrochloride with one previous episode of fever.

Combining the results of the three plans of therapy, of the 30 babies delivered 23 have seronegative reactions, 14 having been followed one to twenty-four months. For results 7 have been classified as failures. The probable good results (23 out of 30) would then be at least 76.6 per cent.

In the routine treatment of syphilis in pregnancy, a direct relationship can be observed in the results obtained and the time in pregnancy at which treatment was started. No such relationship is apparent in the cases of intensively treated patients. Of the 9 mothers who were treated in the first trimester of pregnancy, 7 had babies classified as giving a good response to the treatment, and of the 13 who were treated in the second trimester, 9 delivered babies free from syphilis. Eight mothers were treated in the third trimester, and 7 of their babies were healthy.

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139. Speiser, M. D.; Wexler, G.; Thomas, E. W., and Asher, H. A.: The Rapid Treatment of Early Syphilis During Pregnancy, Am. J. Obst. & Gynec. **49**:214 (Feb.) 1945.

Most authorities have felt that all pregnant women who have or have had syphilis should be treated with each pregnancy, irrespective of previous therapy or the status of their serologic tests. After a nonpregnant patient finished the rapid treatment, no further therapy was given unless a relapse occurred. Thirty-two of the intensively treated patients subsequently became pregnant and received no further treatment. Two had previously been treated for early latent syphilis and 30 for secondary syphilis. Of these 32 patients, 27 delivered healthy babies, 26 at term and 1 after thirty weeks of gestation. Five had spontaneous abortions, of which only 1 was due to syphilis. Of the 27 who had healthy babies, 4 delivered ten to eleven months after antisyphilitic treatment; 8 delivered twelve to seventeen months; 5 delivered eighteen to twenty-three months, and 10 delivered twenty-four months after their intensive therapy. Twenty-five mothers had negative intrapartum serologic reactions for syphilis. All of these had seronegative babies. Two mothers had positive intrapartum serologic reactions for syphilis; 1 baby was seronegative at birth, and 1 was seropositive but became seronegative within one month.

Among the 487 patients with early syphilis treated by Neilson and his co-workers [47] there were 20 pregnant women. These patients received by intravenous drip 900 to 1200 mg. of oxophenarsine hydrochloride over a period of five days. Seventeen of these women were followed until delivery. One miscarriage occurred at three months. Fourteen babies born at term were normal "in appearance," and 2 babies (11.8 per cent) were definitely syphilitic. Two of the 14 normal-appearing babies had positive reactions to Kahn tests but were not yet 3 months of age. The authors point out that the follow-up of treated patients has not yet been long enough for a proper evaluation of intensive chemotherapy.

### CONGENITAL SYPHILIS

*Incidence.*—Kalz [140] attempted to determine the responsibility for the occurrence of congenital syphilis. Is the high incidence of the disease due to ignorance on the part of the mother, to oversight on the part of the physician or to both? The mothers of 74 congenitally syphilitic children in the author's service in Montreal were questioned regarding their antepartum care. In some instances more detailed information was obtained from the physician by whom the patient had been seen. In 17 instances no physician had been consulted during pregnancy, and in 1 instance treatment had been refused. Ignorance of the mothers, therefore, accounted for the birth of 18 syphilitic children. In the remaining 56 cases responsibility rested with the physician. In

140. Kalz, F.: Congenital Syphilis, Canad. M. A. J. **52**:179 (Feb.) 1945.

49 cases no prenatal serologic tests for syphilis had been done; in 5 instances infection occurred in the course of pregnancy and was overlooked, and in 2 cases the physician ignored a report of a positive serologic reaction for syphilis. From this study, Kalz believes that emphasis should chiefly be placed on the education of physicians.

*Teeth.*—Bauer [141] reports a histologic study of the tooth buds and jaws of 4 fetuses and 2 infants with congenital syphilis. Spirochetes were demonstrated throughout the bony structure of the tooth and jaw but were particularly prevalent about and within the tooth buds, a site of intense growth activity. Tissue reaction in the form of plasma cells and fibrosis lagged behind the appearance of masses of spirochetes and did not reach a maximum until after birth. Evidence of any systemic disturbance of calcification, such as occurs in rickets, was lacking in the cases studied. The author believes that the chronic syphilitic inflammation of the tooth sac produces the enamel hypoplasia of the deciduous teeth and, by pressure on the early tooth bud, results in the characteristic distortion of the crown of the permanent teeth (Hutchinson incisor, mulberry molar).

*Bone Lesions.*—Russo and Shryock [142] analyzed the roentgenographic changes in the bones of 46 patients with congenital syphilis. Their ages ranged from newborn to 19 years. Twenty patients were older than 1 year; 6 were from 5 to 12 months of age, and 20 were less than 5 months of age. The serologic test of the blood for syphilis elicited positive reactions in 43 of the 46 patients. In the great majority of the patients there was roentgenographic evidence of a combination of osseous lesions. Periostitis could be detected in 42 patients, osteochondritis in 21, osteitis in 17 and osteomyelitis in 11. There were 5 pathologic fractures.

The most prevalent lesion in very young infants was osteochondritis with assocated periostitis. In older children, osteitis and osteomyelitis, associated with lesions of other types, occurred in almost equal proportions. Diagnosis of syphilitic lesions of bone in older children on the basis of the roentgenologic evidence is more difficult than in young babies.

*Interstitial Keratitis.*—Bilateral interstitial keratitis occurs predominantly in patients with congenital syphilis. The association of

141. Bauer, W. H.: Tooth Buds and Jaws in Patients with Congenital Syphilis: Correlation Between Distribution of Treponema Pallidum and Tissue Reaction, Am. J. Path. **20**:297 (March) 1944.

142. Russo, P. E., and Shryock, L. F.: Bone Lesions of Congenital Syphilis in Infants and Adolescents: Report of Forty-Six Cases, Radiology **44**:477 (May) 1945.

deafness is not uncommon in this group of syphilitic patients. Cogan [143] reports 4 examples of interstitial keratitis associated with vertigo, tinnitus and deafness occurring in persons in whom there were no signs or symptoms of syphilis from the history, physical examination or serologic tests. In 3 patients the clinical observations were identical. All were young women whose presenting complaints were severe vertigo, tinnitus, progressive bilateral deafness, pain in both eyes, ciliary injection, photophobia and somewhat reduced vision. Examination showed nerve deafness with absence of labyrinthine function, a deep keratitis of both eyes characterized by patchy infiltration of the deep corneal stroma, little reaction in the anterior chamber and no apparent abnormalty of the iris. The onset of vestibuloauditory symptoms and of ocular symptoms occurred within a few weeks of each other. The course of the illness was chronic, with progression of deafness, diminution of vertigo and unchanged ocular signs over a two to ten month period. The fourth patient was a man in whom the vestibuloauditory symptoms were relatively mild and the keratitis was unilateral and showed complete remission between attacks, which continued over a period of months. The signs, symptoms and course of the syndrome differ from those of the interstitial keratitis and nerve deafness of congenital syphilis. The etiologic agent is not apparent in the present cases.

Castroviejo [144] discusses keratectomy (the excision of external layers of the cornea) in the treatment of corneal opacities. A brief description is given of the different types of keratectomy utilized by the author. Superficial keratectomy in selected cases offers the ideal method of improving the visual acuity of the affected eye. Not all corneal opacities are suitable for corneal transplantation (keratoplasty). It is in these cases that keratectomy is apparently of principal value.

### SYPHILIS ASSOCIATED WITH OTHER DISEASES

*Tuberculosis.*—The combination of syphilis and pulmonary tuberculosis continues to present difficult problems to the phthisiologist as well as to the syphilologist. Two of these problems, the effects of (*a*) syphilis and (*b*) antisyphilitic treatment on the course of pulmonary tuberculosis in the Negro, are considered by Hoffman and Adams [145] in an analysis of 1,705 adult patients admitted consecutively to a tuberculosis sanatorium. The prevalence of syphilitic infection in this

143. Cogan, D. G.: Syndrome of Nonsyphilitic Interstitial Keratitis and Vestibuloauditory Symptoms, Arch. Ophth. **33**:144 (Feb.) 1945.

144. Castroviejo, R.: Keratectomies for Treatment of Corneal Opacities, Arch. Ophth. **32**:11 (July) 1944.

145. Hoffman, R., and Adams, G. G.: Syphilis and Pulmonary Tuberculosis in the Negro, Am. Rev. Tuberc. **50**:85 (Aug.) 1944.

group as determined by serologic tests was 29.7 per cent, of which 10 per cent was early latent syphilis, 70 per cent late latent syphilis, 15 per cent syphilis of the central nervous system and 5 per cent cardiovascular syphilis. Analysis of the data presented revealed no significant difference between the syphilitic and the nonsyphilitic groups in the amount of pulmonary disease, the predominant type of tuberculous lesion or the percentage of deaths. Of the patients with minimal tuberculosis, 24.7 per cent had syphilis; of those with moderately advanced disease, 29.2 and of those with far advanced disease 31.1 per cent. Since most studies of this nature indicate that the percentage of syphilis is highest in the group with far advanced tuberculosis and lowest in those with minimal involvement, the inference is usually drawn that the presence of syphilis unfavorably affects the patient's resistance to tuberculosis. The authors, taking issue with this viewpoint, suggest that the economic status of the patient is the important consideration.

In respect to the administration of antisyphilitic treatment to tuberculous patients, the authors have a rational approach. Patients with early infectious syphilis and those who are syphilitic and pregnant are treated regardless of the status of their tuberculosis. Antisyphilitic treatment is also administered to those with early latent or late cardiovascular syphilis or neurosyphilis and to those patients, who on admission, "need one or two courses to complete treatment." Patients with late latent syphilis are treated only when the prognosis from the standpoint of tuberculosis is good. The authors are not convinced that the arsenicals exert any deleterious effect on the course of pulmonary tuberculosis. They have observed only a single instance in which they were able to ascribe a flare-up of tuberculosis to the administration of an arsenical drug.

*Diabetes Mellitus.*—The causal status of syphilis in the etiology of diabetes mellitus has long been a controversial subject. Other than in infants with early congenital syphilis, pancreatic lesions which could be ascribed to syphilitic infection have been found only by Warthin, whose studies have never been confirmed. The recent clinical reports of Joslin and of Williams [15] failed to indicate any beneficial effect of antisyphilitic treatment on the course of diabetes mellitus in patients with syphilis.

In a long-term clinical study (follow-up periods of ten to fifteen years), Perkin [146] records observations on 54 syphilitic patients in a total of 550 diabetic patients. The diagnosis of syphilis for these patients was made on the basis of positive serologic reactions for

146. Perkin, F. S.: Syphilis and Diabetes Mellitus: A Long-Term Clinical Study, Ann. Int. Med. **21**:272 (Aug.) 1944.

syphilis in 42, and for 12, with negative serologic reactions, on anamnestic data. The author implies that all patients had late syphilis, the majority of them latent, since late manifestations were found in only 7 (neurosyphilis in 5, benign late and cardiovascular in 1 each) though admittedly few examinations of spinal fluid were performed. In this small series, diabetic patients with syphilis were somewhat older than patients in the nonsyphilitic group and had an unusually mild form of diabetes.

In attempting to evaluate the effect of antisyphilitic therapy on the course of diabetes, 19 patients were studied, 14 of whom in Perkin's opinion showed varying degrees of improvement in tolerance following antisyphilitic treatment; 5 showed no improvement. It is not clear from the report how well other factors were controlled which might influence the course of diabetes. The author states, "In some cases, when feasible, no diabetic treatment, as diet or insulin, was prescribed."

*Gonorrhea.*—Guthrie [147] studied the prevalence and incidence of syphilis among 396 persons who had gonorrhea or had been exposed to it admitted to the Venereal Disease Division of the Johns Hopkins Hospital from Aug. 1, 1942, through May 30, 1943. Persons found to have gonorrhea during routine examination of patients with primary or secondary syphilis were excluded. The author summarizes his observations as follows:

> Thirty-one per cent of gonorrhea patients and 39 per cent of contacts had or had had syphilis on admission. These percentages are not significantly different. Negroes had syphilis three times as frequently as whites; female patients more often than male patients. The age specific syphilis rates in Negroes rose from about 5 per cent in the group under 10 years of age to 50 per cent in the 30-to 39-year group.
>
> One hundred and twenty-eight nonsyphilitic gonorrhea patients were re-examined for syphilis during the twelve weeks following admission. They accumulated 840 person-weeks of observation, and three were observed to have developed syphilis. This relatively low rate at which gonorrhea patients develop syphilis does not justify frequent blood testing. Patients may be inspected for lesions when the necessary observations for gonorrhea are made. Serologic tests for syphilis should be made on admission and at four-or six-week intervals during the next twelve [preferably sixteen, since the advent of penicillin] weeks.

Cameron and Chapman [148] present a study which should shock even the most torpid health department into a soul-searching inquiry as to

147. Guthrie, N. W.: Syphilis in Gonorrhea Patients and Contacts, Am. J. Syph., Gonor. & Ven. Dis. **28**:583 (Sept.) 1944.

148. Cameron, A. R., and Chapman, A. L.: Prevalence of Gonorrhea Among Syphilitic Patients: A Study Made in Delaware in 1943, Ven. Dis. Inform. **25**: 238 (Aug.) 1944.

its present methods of diagnosing and treating gonorrhea. A random survey was made of 412 male syphilitic patients attending venereal disease clinics sponsored by the Delaware Board of Health. Ninety-six per cent were Negroes. No patient was interviewed or examined more than once, and cultures were not available. The reported prevalence of gonorrhea is therefore, in all probability, far below the actual prevalence. Eighty-two (20 per cent) of the 412 patients had a urethral discharge which was positive on spread for gram-negative intracellular diplococci. Fifty additional patients had a urethral discharge reported (on the basis of 1 spread) as nonspecific. Eighty-nine per cent of the patients admitted having had a urethral discharge in the past. This study suggests that the present methods of dealing with gonorrhea are ineffective from the standpoint of diagnosis, treatment and epidemiology.

### YAWS

*Bones and Joints.*—Helfet [149] states that yaws is the commonest disease of bones and joints in the tropics. Whereas syphilis tends to attack the bones and joints slowly and relatively silently, yaws present a more rapid and painful picture in many instances. Symptoms are usually of only a few weeks' duration, during which time striking roentgenographic changes develop. In yaws, a juxta-articular lesion may simulate arthritis of the joint itself, with pain, tenderness, swelling, muscle spasm and limitation of movement. When the shaft of a long bone is involved, a picture resembling septic osteomyelitis may result. The onset of symptoms often follows trauma and may be heralded by fever. The tibia, the lower end of the femur, the inner end of the clavicle and the lower end of the humerus appear to be the sites of election. Roentgenographic examination may show increase in diameter of the bone, considerable increase in density and single or multiple punched-out areas. More frequently, however, in this rapidly progressing type of yaws there is subperiosteal necrosis of the cortex, with raising of the periosteum, and the deposition of periosteal new bone, which in some cases is so dense as to simulate osteogenic sarcoma or the "onion-layering" of a Ewing tumor. Pathologically, the lesions consist of edematous, almost myxomatous-appearing tissue. A microscopic section shows infiltration of small round cells, many plasma cells and perivascular cuffing, but little or no endarteritis obliterans, which is characteristic of syphilis. Yaws tends to attack joints and tendon sheaths as well as bones. It is common to find a patient with ganglions involving the dorsal tendons of wrists or feet.

149. Helfet, A. J.: Acute Manifestations of Yaws of Bone and Joint, J. Bone & Joint Surg. **26**:672 (Oct.) 1944.

In joints the disease is relatively painless, and the joint cartilage is not involved. When treatment with an arsenical drug is administered the response is dramatic. Subjective symptoms subside in one or two weeks, but the actual tumors subside much more slowly. Roentgenographic evidence of consolidation of the lesion can be demonstrated within six weeks.

Juxta-articular nodules have been described in association with syphilis, with the arthritides and with several tropical diseases, notably yaws, filariasis and nocardiosis (a fungous infection). Chambers [150] reports the presence of these nodules in 128 patients observed in rural Jamaica, where yaws is endemic. Of these, 110 gave a history of yaws; only 21 of the 128 patients had received any previous treatment. He points out that the incidence of juxta-articular nodules is highest in yaws-endemic areas farthest removed from centers for treatment (about 1 per cent of the total number of infected persons) and lowest in areas with nearby facilities for treatment. Multiple nodules are the rule, the common sites being elbow and knee joints. The lesions respond slowly to antiyaws treatment, but in the author's experience bismuth subsalicylate was as effective as neoarsphenamine.

*Penicillin Treatment of Yaws.*—Whitehill and Austrian [151] have treated 17 patients with primary or secondary yaws, in all of whom Treponema pertenue was demonstrated on dark field examination before treatment. About 500,000 units of penicillin was administered intramuscularly in doses of 15,000 units, every four hours day and night for five to six days. All of the patients were Fijians. Although 6 of the patients had received previous arsenical or bismuth treatment in each case, the lesions were progressive before the start of penicillin therapy. Patients were hospitalized throughout the period of observation. Spirochetes disappeared from the cutaneous lesions of all but 1 patient within fifteen hours, and in the single exception within forty hours. With one exception all cutaneous manifestations of yaws were completely healed within three weeks after the start of treatment. Serologic reactions were positive in all patients and did not respond over the short period of observation. In an addendum Whitehill and Austrian submit similar results for an additional 25 patients, and a single case of tertiary yaws is reported in detail. In this case the patient had numerous areas of destruction and periosteal proliferation in a number of bones. The patient had been refractory to other therapy

150. Chambers, H. D.: Juxta-Articular Nodules, Arch. Dermat. & Syph. **50**: 105 (Aug.) 1944.

151. Whitehill, R., and Austrian, R.: Treatment of Yaws with Penicillin, Bull. U. S. Army M. Dept., March 1945, no. 86, p. 84.

and was therefore given a total of 1,000,000 units of penicillin in about eleven days. The lesions healed slowly, and therefore after an unstated interval following the first course of treatment the patient received an additional 2,400,000 units of penicillin. Subsequently all cutaneous lesions healed completely, and roentgenologic examination showed bony repair.

Lofgren [152] has also reported the favorable result of treatment with penicillin of a single patient with yaws.

152. Lofgren, R. C.: Yaws Treated with Penicillin: Report of a Case, U. S. Nav. M. Bull. **43**:1025 (Nov.) 1944.

# Correspondence

## ARACHNODACTYLY (SPIDER FINGERS)

*To the Editor:*—Apparently H. Gray's article on "Arachnodactyly (Spider Fingers)" in the April issue of ARCHIVES OF INTERNAL MEDICINE (**75**:215, 1945) can easily be interpreted as a calling to task of the specialties, specifically of ophthalmology. As an ophthalmologist, I should like to attempt some small defense in an endeavor to disintegrate any unwritten misconceptions concerning the specialist's being weaned away from Mother medicine. Unwittingly, this article, appearing in a journal of internal medicine, shows just this shortcoming, for the author has overemphasized linear measurements at the expense of medicine, surgery, orthopedics, genetics and ophthalmology, and has attempted to replace the investigator's eyes with dimensional analyses.

In order to support these allegations it is necessary to elaborate on some, but by no means all, of the discrepancies which appear in the article, for they might be digested with facility and assimilated as readily unless they become irrigated first with the well known saline solution.

For example: The author mentions feeblemindedness as one of the characteristics of the syndrome, the statement being made rather innocuously. Nevertheless, in a review of 204 cases, Rados (ARCH. OPHTH. **27**:477 [March] 1942) stated, "As a rule, the nervous system escapes implication. The general intelligence often is particularly good." In the 204 cases reviewed by this same author an occasional patient was shown to have some mental retardation but not any degree of feeblemindedness. An outstanding characteristic of these cases is the senile, sad, aged and melancholy facial expression, which for some unknown reason has been confused with the patient's mentality. The case reports certainly do not show any reason for inserting feeblemindedness in the syndromic triad.

In another paragraph Dr. Gray states: "In some of the reports of cases the diagnoses were not warranted by the measurements given; in many of the cases the measurements were fragmentary, perhaps only of one finger or of one phalanx, and, finally, in most cases the landmarks used were so obscure as to prevent comparisons by the reader."

Should it be pointed out that the diagnosis is not determined by any measurements? The syndrome is strikingly apparent and requires only a vague recollective knowledge of its cardinal signs to be recognized. It is true that most of the cases reported in the literature are either of the clearcut, typical variety (typus Marfan) or of the forme frustre grouping. The latter class of necessity has questionable dimensions. As implied by the terminology, such a classification indicates that this is to be anticipated, since these cases are incomplete genetic problems which we have not as yet satisfactorily explained. Measurements in such a group could not conform to any fixed pattern. There are cases reported in which there is symmetric bilateral lenticular subluxation with certain skeletal defects associated with melancholic expression in the absence of arachnodactyly.

Measurements according to Gray's standards and their interpretations would result in discarding these from the syndrome even as so-called forme frustre cases. This in turn would lead to a lack of understanding of the underlying cause of the syndrome and would not aid in clarification of the present concept of the cause of Marfan's syndrome, namely, so-called genetic coupling. At present, it is believed

that a switching of certain elements in the genes of the chromosomes is the factor most likely to be responsible for the appearance of the atypical cases of Marfan's syndrome.

Besides the typical cases in which the syndrome is of complete development, there are incompletely developed cases in which the general habitus recalls the typical picture, although not all the cardinal symptoms of the syndrome are present. A symptom complex may be shown to be grouped around a central dominant characteristic which in the case of Marfan's syndrome is the marked slenderness or gracility of the extremities. There, different single symptoms grouped about the dominant characteristic are caused not by multipotential genes but by genes located close to one another within the same chromosome (Marfan, M. A.: Un cas de déformation congénitale des quatres membrés, plus pronouncée aux extrémités, characterisée par l'allongement des os, avec un certain degré d'amincissement, Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220, 1896).

In still another paragraph the author maintains: "Similar statements are common about reported cases but should be regarded skeptically; more than once 4 instances in the same family have been reported . . . hence it is probable that a number of instances in the literature stated to be isolated could have been demonstrated to be really familial if measurements had been made of the immediate relatives."

Some of the greatest ophthalmologists, among whom must be included Weve, Irgersheimer, Fleischer, Hamburger, Vogt, Franceschetti, Sorsby, Amsler, Coppez, Buecklers, Passow and Viallefonte, must be guilty of failure to recognize the really familial nature of this disease because they did not measure the skeletal structure of the relatives. This indeed would be very strange, for among these ophthalmologists are included men who have contributed much in the field of genetics as well as in that of congenital ocular anomalies. These men, trained to see microscopic similarities and differences not only in the eye but also in the chromosome should be able to detect the familial likenesses of freaks such as those with the Marfan syndrome without having to conduct intricate anthropologic measurements, since the habitus of the Marfan syndrome causes the laymen to stop and look with mouth ajar.

The author in reporting case 1 stated that "his hands, feet and ears were noted at once as large, and the nurses called him 'infant Hercules.'" Since in 80 per cent of the cases the patients have subluxated lens and in 50 per cent they have a congenital cardiac condition—why not just check "Hercules" for these conditions?

At this point it might be worth while to mention that from the very first case report (that of Marfan previously cited) the hereditary character of the case was suspected. In the earliest cases reported there is evidence to show that the hereditary nature of the condition was suspected, for the case reports point out in detail "that a brother of one patient had a congenital cataract and that one of the patient's sisters had remarkably large hands as did a maternal grandfather."

In his summary the author states: "a new contribution to the knowledge concerning this anomaly was made through a careful study of physical build by means of anthropologic measurements."

In reviewing this original contribution the author has made, and after divorcing the mathematic and indicial "confusors," it appears that the following claims have been made: (a) "microcephaly—apparently a new finding in connection with arachnodactyly"; (*b*) an amazing disproportion between the upper and lower ends of the trunk; (*c*) "the length of the patient's hands as a whole . . . and the slenderness of the hand"; (*d*) slenderness of the foot. (*e*) "Arachnodactyly manifests a partial gigantism in the upper limb, which is not of like degree in the three

segments, but progressively more pronounced as one proceeds away from the body. For the lower extremity . . . the reverse is found."

As regards microcephaly as a new finding—this is true only of 1 case, namely, the author's. Other cases show a distinct tendency toward dolichocephaly, which is the usual thing, although an occasional case of brachycephaly has been reported.

The author states that an amazing disproportion between the upper and lower ends of the trunk exists, and the biacromial to bicristal ratio is so striking as to occur in less than 1 to 1,000 cases. Both these claims are new ones and should be looked for. They produce such striking pictures that they should be recognized readily without mensuration.

The other claims of the author have long ago been emphasized in the literature. The length and slenderness of both hands and feet and elongation of the upper extremity have been best expressed by stating that the patient's span exceeded his height and that the hands were extremely gracile. The reverse phenomenon for giantism in upper and lower limbs in the three segments has been described only in a single case.

From scrutiny of Gray's photographs certain features of importance in the syndrome may be gleaned which received no mention from the author. They include: (*a*) sparsity of subcutaneous fat; (*b*) bowing of elbows; (*c*) overlapping of toes, and (*d*) webbing of fingers.

In conclusion, I wish to refer the author and all readers interested in Marfan's syndrome to the excellent article written by Rados, a very careful review in which every one of the 204 cases reported up to that time is analyzed and, in addition, a very complete and satisfactory anthropologic tabulation appears. Furthermore, Rados' conclusion may be worthy of emphasis: "The arachnodactylic habitus is extremely obvious."

692 High Street.

E. ROSEN, M.D., Newark, N. J.

# Book Reviews

**Rypins' Medical Licensure Examinations.** Edited by W. L. Bierring, M.D. Fifth edition. Price, $6. Pp. xxii + 546. Philadelphia, London and Montreal: J. B. Lippincott Company, 1945.

President Lowell of Harvard once remarked that examinations, like most human beings, are imperfect and that their results are only approximate. Harold Rypins, like Mr. Lowell deeply tinged with Harvard crimson, apparently agreed with this philosophy, for in 1933 he wrote the first edition of this book.

The preface to the first edition still lives and must be studied to appreciate why a fifth edition ever proved necessary. Rypins believed that the average graduate of an American medical school is well prepared for the practice of his profession yet needs assistance in the use of the material with which his head has been filled by his professors in order to make of examinations a relatively pleasant undertaking to be faced without trepidation. Accordingly, he attempted to prepare a serious and orderly summary of such parts of the medical curriculum as are ordinarily considered important by various examining boards.

The success of the venture was notable. Until 1939 new editions were forthcoming at two year intervals. The fifth edition, under a new editor, has just appeared.

Rypins attempted to bring each edition up to date and to avoid unnecessary words. This plan has been adhered to, so that the latest edition, while modern, is not much larger than was the first. Rypins divided his book into twelve chapters —an arrangement which has been maintained. The new edition has acquired eight eminent collaborators, who have helped materially to strengthen the work.

*The Journal of the American Medical Association* (**101**:1100-1101 [Sept. 30] 1933) reviewed the first edition, and what was said of the book then is true today. It is a unique volume. Its text is clear and concise. It does not pretend to be a complete textbook or to teach anything new. Its only object is to assist any student in the intelligent and practical use of what he knows. It should be helpful for this purpose.

**What to Do About Vitamins.** By Roger J. Williams. Price, $1. Pp. 56. Norman, Okla.: University of Oklahoma Press, 1945.

This is a satisfactory little book to recommend to patients or other laymen interested in and wishing information about foods and nutrition. The author provides practical, easily understood directions on how to choose foods so that the taking of extra vitamins is unnecessary. Good diet planning demands more attention than many have supposed. It is necessary because of the prominent position in the food environment of refined fuel foods that fail to carry their share of the "lubricants" (vitamins and minerals) required for good health. The food producer, by raising the nutritional quality of his products, should play an important part in improving the diet of the public, and "the time should come when the housewife will not have to exercise as much caution as she does now, and when she can, by the simple expedient of diversifying her purchases, furnish her family with a completely adequate as well as attractive diet."

The author, Roger J. Williams, director of the Biochemical Institute of the University of Texas, is one of the leaders in the biochemical research which has contributed so greatly to the current knowledge of nutrition. He is best known for his discovery, in 1933, of pantothenic acid and, more recently, of folic acid.

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